RC PSYCH
ROYAL COLLEGE OF PSYCHIATRISTS

CR206

Prescribing anti-epileptic drugs for people with epilepsy and intellectual disability

COLLEGE REPORT

College Report CR206

October 2017

Approved: August 2017

Due for revision: 2022

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Foreword

This report addresses the extremely important area of epilepsy in the field of intellectual disability (ID), also known as learning disability. Epilepsy and ID are two conditions that carry stigma and can lead to social isolation. An individual who experiences both these problems faces huge challenges.

Anti-epileptic drugs (AEDs) are the main form of treatment for epilepsy. In people with ID, response to treatment can be poor and surgical options are limited. Approximately 20–25% of people with ID have seizures. With increasing severity of ID, the association of seizures and other physical conditions rises. People with ID constitute nearly 25% of the total population with epilepsy and 60% of the population with treatment-resistant epilepsy. Mortality rates due to epilepsy are recognised to be higher among people with ID than in the general population. The economic impact of providing treatment is significantly higher than in the general population. People with ID are five times more likely to present to emergency departments for seizure-related problems.

Epilepsy care in recent years has seen a large range of evidence-based treatments and interventions. As expectations held by people with ID and their families with regard to services rise, there has simultaneously been a transformation in thinking about how people with ID should be treated in the context of vulnerabilities arising from cognitive deficits, social exclusion and the high rate of comorbidity.

Epilepsy management is recognised as a core skill needed by psychiatrists working with people with ID. It is vital that psychiatrists for this population understand the complexities of their physical and mental health needs. This includes interactions between AEDs and other commonly used medication and knowing how to identify and manage side-effects. In addition, they need to make difficult choices for people who struggle to make their own decisions and have problems in communication. All this must be achieved while ensuring a satisfactory quality of life for their patients.

I welcome this report, which has put together a clear, useful and detailed evidenced-based practical prescribing guide that will improve the lives of people unfortunate enough to have both ID and epilepsy.

Professor Wendy Burn
President, Royal College of Psychiatrists

Scope of this report

This report aims to provide epileptologists, psychiatrists, doctors and clinicians working with people with ID and epilepsy an overview of good practice prescribing. Its focus is on using current evidence and applying it to support practical prescribing for people with ID. The document is not a substitute for recognised prescribing guides such as the *British National Formulary* (BNF). It is not a complete or comprehensive overview of epilepsy management or of epilepsy service provision. The contents of this report need to be considered as guidance, especially where most practitioners struggle when the evidence does not inform the complex clinical challenges. The report is a consensus statement on the application of current evidence used in the general population to people with ID and should be used for the purpose of guiding holistic decision-making in prescribing AEDs. It is important that clinicians keep themselves up to date using the latest information on the subject as part of their continuing professional development, as the subject area covered by this report changes rapidly.

Executive summary

The most vulnerable people in society deserve the best healthcare. The recent release of the national Stopping Over-Medication of People with a Learning Disability, Autism or Both (STOMP) pledge was a significant contribution in giving direction to the manner in which prescribing should happen for people with ID. Although STOMP concerns itself with psychotropics it has opened the door to the possibilities and potential for other medical specialties to follow suit in the way they take care of people with ID.

People with ID have much higher rates of epilepsy than the general population, their epilepsy is more difficult to diagnose and treat, is more likely to be treatment resistant and require polypharmacy, and patients may find it harder to communicate their needs and wishes. The evidence for the efficacy of treatments in this subpopulation is less strong. Together, these factors culminate in higher premature mortality and morbidity rates among people with ID and epilepsy.

The limited current evidence on AEDs is most supportive of sodium valproate and lamotrigine, moderate for topiramate, gabapentin, perampanel, levetiracetam, rufinamide and lacosamide, and does not support the use of vigabatrin, phenytoin and phenobarbitone. Carbamazepine too has very limited evidence, but has real-world experience and use in its support. Benzodiazepines are very useful as rescue medication and for short-term use, but rarely beneficial in long-term use. Specific exclusions apply for a number of AEDs that have been shown to be of more value in treating certain rare conditions associated with ID and epilepsy. Many of the newer AEDs need further research before an informed judgement can be made. A 'traffic light system' using current evidence and expert views has been put in place for commonly used AEDs to highlight specific advantages and disadvantages for use in people with ID.

When prescribing AEDs, start with a low dose and titrate upwards slowly. The priority must be to minimise side-effects during initiation of the drug, so that patients and carers gain confidence in it. We propose algorithms based on evidence in focal and generalised seizures. The safety of the patient should be considered before treatment efficacy and outcomes, and we propose 10 guiding principles of prescribing for people with ID.

Difficulties in diagnosing epilepsy in people with ID arise because of physical and psychiatric comorbidity, complex behaviours, difficulties performing investigations and challenges in communication. In addition, patients are more likely to have comorbid mental illnesses and are at greater risk of iatrogenic harm from treatment. We highlight the common issues that should be considered by any prescriber of AEDs for people with ID, including special subpopulations of autism and dementia.

People with ID are more vulnerable to, but less able to communicate, side-effects of AEDs. These include effects on cognition (phenytoin and topiramate), weight gain (valproate, gabapentin and pregabalin), weight loss (topiramate and zonisamide) and osteoporosis (multiple AEDs). These medications can also cause behavioural disturbances, and certain AEDs show differences between different brands of the same drug, and awareness of these needs to inform prescribing. Clinicians should also remember the risk of drug interactions, especially between different AEDs and with psychotropics and contraceptives. We provide a framework for considering this. The relevance of genetic testing is also presented.

Psychotropic medications , especially antipsychotics, can increase the risk of seizures. First-generation antipsychotics confer a marginally greater risk than second-generation, and aripiprazole has the lowest risk of inducing seizures. Antidepressants are less risky, but those that are most sedating are most likely to lower the seizure threshold. Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) are best avoided as selective serotonin reuptake inhibitors (SSRIs) have lower risks in epilepsy. Lithium can cause seizures in overdose. Remember the interactions between psychotropic medications and AEDs. We give an overview of these.

Every effort should be made to communicate information in a person-centred manner with patients and carers. Patients should be reviewed at least annually and, if changes are being made to AEDs, preferably every 3 months. If patients are on three or more AEDs, clinicians should be more vigilant. They should also be alert to any changes in the patient's health risk status. If the individual lacks decision-making capacity, their best interests must be considered. This would include the benefits versus the risks of changing AEDs. The clinician should rationalise what a proposed change is expected to achieve, taking into account the potential for success, history of previous AED failures, treatment resistance, side-effect sensitivity, patient and family/carer experience, etc. Any change from one AED to another should involve an overlap of titrated medication to avoid the risk of seizures. The presence of ID does not exclude attempts to withdraw anti-epileptic medication, but this should be done with caution and close medical monitoring. This report provides practical guidance on initiation, monitoring, reviewing, switching and withdrawing of AEDs in people with ID.

Psychiatrists are in an excellent position to improve the management of epilepsy in people with ID. They are holistic and comprehensive in their approach, have good communication skills and are aware of pharmacological complexity. Importantly, they work within multidisciplinary teams and have a good understanding of psychological and social issues that require addressing in illness management. There is need for further research on the use of AEDs in people with ID, and hopefully psychiatrists will lead this research with their neurological and neuroscience colleagues.

Every attempt has been made to ensure that the best-quality evidence and experts in the field were consulted in the preparation of this report. Their feedback and input has, in our view, made the report consistent, richer, holistic and person-centred. This document is an effort to provide a pragmatic and practical bridge over the yawning gap in evidence in this area. Its principal purpose is to help colleagues working with people with ID and epilepsy to be aware of current issues and concerns and to encourage them to take a more active and informed role in all-inclusive management not just of the ID-related problems or the epilepsy, but of the individual's overall care. This report, however, is not a substitute for a definitive prescribing guide such as the *British National Formulary* (BNF), which should form the bedrock of any prescribing. We recommend that complex case management involving particular medication matters be carried out in consultation with a pharmacist and, where possible, discussed with a peer group.

Guiding principles

The following principles should be kept in mind when prescribing AEDs for people with ID.

1. Follow best practice guidelines for the diagnosis of epilepsy and make reasonable adjustments to ensure access to the necessary investigations, including genetic testing if it might be informative.
2. Deliver person-centred care and consider the needs and wishes of the individual.
3. Consider providing longer clinic appointments.
4. Try to provide individuals and carers with suitable information at a level they can comprehend, such as easy-read literature.
5. If the individual lacks the mental capacity to make informed choices, consult with key stakeholders in the person's best interests and provide relevant information on medication, especially its effects and side-effects.
6. Define seizure improvement for the individual and agree on a method of monitoring and reporting it.
7. Make medication choices informed by the evidence base described in this report – tailor medication to the individual's particular diagnosis and syndrome, and consider comorbidities and other current medication.
8. If medication is ineffective, consider alternative diagnoses, including non-seizure related movements that mimic epilepsy (such as tics), stereotyped behaviours of autism, and non-epileptic attack disorder.
9. Set in place ways of gathering feedback, including effect on mood, behaviour and social life, to be considered at regular structured reviews.
10. If the individual lacks capacity and is showing treatment resistance or there is ambiguity regarding the role of medication, strongly consider convening a best interests meeting. Key stakeholders should include family/carers/independent mental capacity advocate, general practitioner, other health and social professionals. The person's wishes need to be gathered as best as possible to inform the meeting. Questions to consider include: What is the current situation? Is treatment change warranted now? If so, what? If not, why not? When would change to the individual's AEDs be needed in the future and why? Records must be kept and the decisions re-visited at a set and agreed time.

This is not an exclusive list. Other patient-centred factors that should be considered are outlined in this document, and each guiding principle is discussed in more detail.

Background

There is a strong association between epilepsy and ID and both may be linked to a wide range of pathological processes (Forsgren et al, 1990; Bowley & Kerr, 2000; Lhatoo & Sander, 2001). The prevalence of epilepsy in the general population is between 0.5 and 1% (De Boer et al, 2008). In contrast, 20–25% of individuals with ID have epilepsy (Ring, 2013; Robertson et al, 2015). There is also a direct proportional relationship between severity of ID and prevalence of epilepsy (Richardson et al, 1981; Steffenburg et al, 1995). Up to 50% of people with moderate to profound ID have epilepsy, and half of these are resistant to treatment with current AEDs (Ring, 2013).

Epilepsy results in significant morbidity and mortality and has a wider impact on the individual's everyday life and on family and caregivers (Hannah & Brodie, 1998). Alongside aspiration pneumonia, seizures are the leading cause of preventable death in the population with ID and the main cause of potentially avoidable hospital admissions (Rodway et al, 2014). The two major epilepsy-related causes of death among people with ID are sudden unexplained death in epilepsy (SUDEP) and status epilepticus, which are significantly overrepresented in this population (Kiani, 2014; Devinsky et al, 2016).

Understanding the complexity and individual needs of people with ID highlights some of the barriers they face in accessing appropriate care and treatment (Table 1). Communication problems affect the reliability of assessments and diagnosis. Clinicians often have to consider treatment options in cases where individuals lack the capacity to make informed decisions regarding their treatment. The ID population also has significantly higher levels of comorbid mental and physical disorders, which may influence treatment choices (Cooper et al, 2007; Kwok & Cheung, 2007; Heslop et al, 2013). There are no specific national guidelines for ID, but both the National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) recognise the problem with prescribing for this group. Two previous documents have reviewed prescribing for epilepsy in people with ID and reached a consensus on management (Working Group of the International Association of the Scientific Study of Intellectual Disability, 2001; Kerr et al, 2009). Both conclude that there is a dearth of high-quality evidence from well-constructed studies on which to base definitive guidance. The potential adverse effects of AED treatment on cognition and behaviour are not considered specifically in the population with ID in current national guidelines. Equally, the practical nuances of administering certain drugs in this vulnerable population needs highlighting. It is also worth noting that different drugs have different levels of evidence of efficacy on seizures

Table 1 Common features of epilepsy in people with ID in comparison with the general population

- Seizures are usually present in early life
- Higher rates of genetic/structural brain damage, with generalised rather than complex partial seizures being the most common
- Less likely to be seizure free on first treatment and more likely to have life-long seizures
- More sudden unexpected death in epilepsy (SUDEP) and status epilepticus
- Higher rates of AED prescription and polypharmacy
- Higher risk of status epilepticus and thus more likely to be on an emergency rescue protocol
- Increased rates of attendance at emergency departments
- Multi-morbidity
- Individuals may have limited ability to communicate and make treatment choices
- No clear mechanism of measuring treatment 'success'
- Specific problems with chewing, swallowing, constipation and percutaneous endoscopic gastrostomy (PEG) feeding

in people with ID. Other neurodevelopmental, cognitive, mental and physical comorbidities may also influence seizure presentation and the choice of medication, its side-effects and outcome.

There is a clear need for a consensus document to provide an overview of the current evidence base for the prescription of AEDs for people with epilepsy and ID. There is also a need to identify the gaps in our knowledge of prescribing to ensure that clinicians, people with ID, carers and families are fully informed of the benefits and risks associated with prescribing, or advising against, treatment. This report will largely focus on providing practical and good practice advice on prescribing of anti-epileptic medication.

When considering when and how to treat seizures the current evidence must be taken into account. There is limited robust research involving people with epilepsy and ID. The choice of medication is therefore largely based on data extrapolated from randomised controlled trials (RCTs) in the general epilepsy population. Only a few seizure syndromes (epileptic encephalopathies) associated with the development of ID have had specific research. These include Lennox–Gastaut and Dravet syndromes, which are associated with treatment-resistant epilepsy, drug sensitivity, frequent seizures and multiple seizure types, for which an evidence base for guidelines exists (Guerrini et al, 1998; Besag, 2011).

An authoritative report published in 2014 proposed a framework for enhancing the delivery of support for people with epilepsy and ID and

identified four major areas of concern (Kerr et al, 2014). One of the areas highlighted was diagnosis and medical treatment. The report emphasised specific concerns about the prescription of AEDs and the identification and monitoring of side-effects. As part of a strategic response, in May 2017 the Royal College of Psychiatrists' Faculty of Intellectual Disability produced a College Report (CR203) highlighting good practice in the management of epilepsy in adults with ID (Royal College of Psychiatrists, 2017). The report called for further specific advice on the prescription of AEDs for people with epilepsy and ID. The current report on prescribing AEDs for people with ID is the 'next step' in this strategy to improve the standard of epilepsy-related healthcare for this vulnerable group. The scope of this report is to establish best practice for the management of epilepsy with AEDs and the identification of their side-effects. Specific attention will be paid to addressing drug interactions because of the high level of comorbid conditions in this population. This summary of the evidence will help inform prescribing clinicians in relation to the attaining the Bronze/ Silver/Gold competencies laid out in CR203.

Objectives and methodology

The Royal College of Psychiatrists' Faculty of Intellectual Disability notes that an understanding of prescribing for people with epilepsy is essential to the role of a psychiatrist working with such individuals (Royal College of Psychiatrists, 2017).

Objectives

- To identify the current evidence base on prescribing AEDs to people with ID
- To identify the general and specific needs and requirements of people with ID who have epilepsy, with particular focus on the impact of AEDs
- To identify and deliver a framework for evaluating current AEDs, bringing together evidence and expert clinician perspective
- To identify a prescribing framework for psychiatrists treating or being consulted about a person with ID and epilepsy
- To give an overview of the complex side-effects of AEDs and possible ways to mitigate them
- To highlight the practical pitfalls in co-prescribing, including drug interactions with other commonly prescribed psychiatric medication
- To provide a document that psychiatrists might use to measure their current ability to manage epilepsy in people with ID and to develop epilepsy competencies as proposed in CR203 (Royal College of Psychiatrists, 2017)
- To provide a template for a national dialogue with other key health professionals, including specialist epilepsy nurses, neurologists and GPs, with the aim of developing a unified strategy for treatment and management of epilepsy in people with ID to help improve outcomes

Methodology

A recent study (Ford & Norrie, 2016) highlighted concerns that clinical trials are inadequate to inform routine clinical practice, as trial settings are usually unrepresentative of real-life scenarios. There are concerns that clinical trials underestimate the harms while overestimating the

benefits of interventions. There is a call to deliver evidence using pragmatic real-world information with gold-standard proof. Evaluation of effectiveness needs a broad view to ensure that interventions are safe, beneficial and cost-effective in subgroups of the population.

The Advisory Committee of this report recognised that there is a paucity of good evidence for prescribing AEDs for people with ID. However, as there is a growing need to provide practical direction, an attempt has been made here to combine published evidence with the everyday practice of experts in the field to provide a practical guide to prescribing for this population. Development of this report was carried out as follows.

Step 1 – A focused literature review by the Deputy Editor and Editor using recent publications (e.g. Kerr et al, 2014, 2016; Jackson et al, 2015; Doran et al, 2016; Shankar et al, 2017a,b). They also reviewed and analysed best practice documents from organisations such as NICE and SIGN, and recent government White Papers about epilepsy and ID.

Step 2 – The Deputy Editor and Editor wrote a draft report that included a proposal for systems of rating AEDs using a traffic light system.

Step 3 – Circulation of the draft report and extensive feedback from the Advisory Committee (comprising three expert neurologists specialising in epilepsy, including two academics; one specialist epilepsy nurse; four specialists in ID and epilepsy; one GP; one pharmacist; one consultant in general adult psychiatry; and three consultants in ID). Feedback was collected and assimilated into the developing document and plan. The Advisory Committee represented a diverse group of experts in research methodology, research in ID and AEDs, research in epilepsy and clinical experts.

Step 4 – An update on the planned structure of the document was presented at a meeting of the Royal College of Psychiatrists' Intellectual Disability Faculty Executive. Approval was gained to continue in the direction identified and specific issues were highlighted.

Step 5 – The report was circulated to all Advisory Committee members for comments and feedback.

Step 6 – The Faculty of Intellectual Disability submitted the report to the College for stakeholder feedback. It was disseminated to all divisions and faculties; the Psychopharmacology Committee, Northern Ireland Faculty and Faculty of Old Age Psychiatry returned comments.

Step 7 – Feedback received from these stakeholders was incorporated to produce the final report.

Summary of evidence

The decision of when and how to treat epilepsy should take into consideration the impact of seizures on the patient versus the potential positive and negative effects of medication. Treatment with AEDs may not be straightforward; there is the potential for side-effects, toxicity and pharmacological interaction with other drugs. A clear diagnosis of a seizure disorder must be established before initiating pharmacological treatment. Prescribing clinicians should refer to standardised national guidelines for the management of epilepsy from NICE (CG137: NICE, 2012) and SIGN (SIGN 143: SIGN, 2015). These guidelines are based on the same evidence and there are significant overlaps in recommendations. The NICE CG137 guidelines are referred to throughout this report and we attempt to extend advice beyond the scope of those recommendations. We put forward further recommendations that argue that the treatment of people with epilepsy and ID requires specific consideration and guidance owing to the complexity of need.

The assessment of suspected seizures in an individual with ID may be complicated by their level of cognition and communication. As a result, the clinician may be reliant on witness reports from family members or caregivers. The degree of dependence on this information will be influenced by the level of adjustments that both clinicians and services put in place to help communication with the individual. Although the diagnosis of epilepsy is based on the history and eye-witness reports, people with epilepsy and ID should have access to the full range of electrophysiological investigations and neuroimaging to aid assessment and improve accuracy of diagnosis, if this is appropriate. The use of video electroencephalogram (EEG) and telemetry can be particularly useful for this population (Kerr et al, 2001).

When considering treatment options it is essential to adopt a person-centred approach. Seizure type, seizure syndrome and, importantly, patient and carer choice must all be evaluated. Clinicians should aim to profile treatment to take into account specific aetiological risk factors. There is a relatively high incidence of treatment-resistant epilepsy in the ID population. Making an evidence-based informed decision about the most appropriate first-line pharmacological therapy is essential. The most recent Cochrane Review highlights that to date the evidence of the efficacy of specific AEDs in people with ID is generally poor and there are limited robust reproducible outcomes (Jackson et al, 2015).

Most data on the pharmacological treatment of epilepsy in the ID population are derived from open or observational non-randomised trial designs. The results from such trials are open to methodological

criticism and hence interpretation is difficult. There are some exceptions to this. Infantile spasms, Dravet syndrome and Lennox–Gastaut syndrome are common epilepsy syndromes strongly associated with ID, and there has been more extensive pharmacological research into the efficacy of treatment in these syndromes (Table 2).

Table 2 Examples of common epilepsy syndromes associated with ID

Epilepsy syndrome	Evidence for AED role
Dravet syndrome (severe myoclonic epilepsy)	Lamotrigine, phenytoin and carbamazepine can aggravate seizures (Guerrini et al, 1998)
Lennox–Gastaut syndrome	Rufinamide was suggested as offering most benefit (Besag, 2011)
	Lamotrigine was linked to significant seizure reduction and improvement in mood, sociability (Motte et al, 1997)
	Clobazam has had two randomised controlled trials and is suggested to be a good adjunct for drop attacks (Conry et al, 2009; Ng et al, 2011)
	Topiramate has been recognised to have an effect on drop attacks (Sachdeo et al, 1999)

Evidence of the use of specific AEDs in people with ID

Benzodiazepines

There is good evidence to support the use of benzodiazepines (e.g. clonazepam, clobazam, diazepam and midazolam) as emergency rescue and add-on medication in treatment-resistant epilepsy. Midazolam is used extensively to curtail seizures outside of the hospital setting (Walker & Shrovon, 2015), and clobazam is regularly used for people with ID.

Benzodiazepine treatments have been criticised for potential adverse side-effects, including cognitive impairment in long-term use in both general and ID populations, and as a result are favoured more for use as rescue treatments (Isojärvi & Tokola, 1998). The use of benzodiazepines is limited in the presence of cognitive deficit or behavioural disorder. Tolerance is a major concern in people with ID: they might not have active medication reviews and would not be aware of a need for one; a benzodiazepine might have been prescribed for behaviour management and not withdrawn; and if multiple AEDs are prescribed, benzodiazepine tolerance might not manifest as increased seizures. It has been suggested that around 30% of people with epilepsy on clobazam could continue without developing tolerance (Remy, 1994; Purcarin & Ng, 2014). The potential downsides of tolerance include the distress of changing medication and the need to reduce slowly if tolerance occurs.

Another risk is that significant numbers of people with ID find themselves on various benzodiazepines to treat behaviour, mood or anxiety. Clinicians must be aware of the overall 'benzodiazepine load' when prescribing clobazam and other benzodiazepines and monitoring for seizures.

To date, there are no definitive studies or recommendations to guide treatment using this group of drugs in people with ID.

Clobazam

Clobazam has an evidence base especially in Lennox–Gastaut syndrome, and is useful in managing atonic seizures (drop attacks).

It is a unique benzodiazepine as it has a 1,5 benzodiazepine structure (the others all have a 1,4 structure) and it is consequently not as sedative as the other benzodiazepines. It also has a long half-life of 50 hours (active metabolite). It is *not* a drug to be considered for long-term use, but there is evidence to support its use as a rescue treatment for cluster seizures, and as an adjunct for all seizure types in intermittent short-term treatment (up to 5 days in 15-day cycles) (Gauthier & Mattson, 2015). It is therefore the ideal drug to use as a rescue medication where there is a known seizure trigger or where medication changes are occurring and there is a need for some additional 'cover'. Any long-term regular use has to be weighed against the potential of habituation or tolerance, difficulty in withdrawal and long-term side-effects. Due consideration needs to be given to explaining the benefits versus risks of long-term use and, in those lacking mental capacity to make informed choices, a best interests process is advocated.

Carbamazepine

The evidence for prescribing carbamazepine in ID populations is poor. There are no direct studies on the effect of the drug in people with ID. A double-blind RCT reported possible better efficacy in people with ID for slow-release preparations as opposed to regular preparations (Kaski et al, 1991). Carbamazepine is known to have a number of adverse effects; the most common of these is hyponatraemia in up to 40% of people taking the drug. Other side-effects include drowsiness, nausea and vomiting, dizziness and bone marrow suppression. Carbamazepine can also interact with many other drugs prescribed for chronic conditions. As a result of these potentially 'silent' side-effects and interactions it needs to be used with caution in people with moderate to profound ID. This vulnerable group with epilepsy are likely to be treatment resistant and to have multiple chronic conditions treated with numerous medications, all of whose interactions might need to be kept in mind.

Clobazam: see Benzodiazepines

Gabapentin and vigabatrin

The efficacy and safety of gabapentin (in comparison with lamotrigine) were assessed in a randomised open-label study involving 109 adults with ID and treatment-resistant epilepsy (Crawford et al, 2001). Safety and tolerability were assessed using adverse event reports. The overall incidence of adverse events was similar across the treatment groups, with adverse events reported for 62% of participants on gabapentin and 50% on lamotrigine; serious adverse events were reported for 10% on gabapentin and 11% on lamotrigine. This was the first-reported

randomised trial for add-on anti-epileptic medication in people with epilepsy and ID. It concluded that both drugs were effective for seizure control and that neither caused significant worsening of behaviour as evidenced using the Whelan & Speake Challenging Behaviour Rating Scale.

A case review of the first 51 people with Lennox–Gastaut syndrome prescribed vigabatrin, lamotrigine or gabapentin suggested that all three had some positive effect on seizure control. Vigabatrin was associated with higher risk of adverse effects on behaviour, and lamotrigine was associated with increased seizures in a quarter of participants (Bhaumik et al, 1997). Vigabatrin had previously been associated with the development of visual field defects, but the review does not comment on this. The prescribing of vigabatrin for people with ID raises serious ethical concerns, as the BNF states that all patients prescribed vigabatrin must be made fully aware of the risk of visual field defects and how to report these to their physician.

Levetiracetam

To date, levetiracetam has not undergone an RCT within the ID population. A number of open-label studies have demonstrated that it is effective and equally well tolerated in individuals with ID. In one open study, 64 people were given add-on levetiracetam after a 3-month baseline (Kelly et al, 2004). Of these, 24 people (38%) became seizure free and there were a further 18 responders (≥50% reduction in seizures). In general, levetiracetam has been shown to be well tolerated. There is an association with neuropsychiatric disturbance, particularly aggression. This may, however, be confined to those biologically vulnerable with a psychiatric history (Mula et al, 2004) and may be the result of rapid dose escalation, as it has generally been reported more frequently in neurology clinics than in ID clinics.

Lamotrigine

Lamotrigine is a well-tolerated and effective AED for people with ID, and it is thought to have mood-stabilising properties. Early research involving 34 people with ID showed a significant improvement in seizure control in over 50%, with a further 35% becoming seizure free (Buchanan, 1995). Results of a randomised open-label study investigating the use of lamotrigine and gabapentin in adults with ID and treatment-resistant epilepsy suggested that there was an approximate 50% reduction in seizures in half of the people receiving either drug. Both drugs were equally well tolerated and associated with improvements in challenging behaviour. These outcomes have been consistently repeated for lamotrigine in a number of more recent case-series studies. A proportion of the population with treatment-resistant

epilepsy have, however, shown no improvement in seizure control (Bhaumik et al, 1997; Gidal et al, 2000). Lamotrigine has also been subject to the most rigorous quality-of-life evaluation in people with Lennox–Gastaut syndrome, during a randomised placebo-controlled add-on trial with 169 participants. An improvement in seizure control was observed, with a significant reduction in atonic seizures (drop attacks) and total seizures. Outcomes also demonstrated significant improvement in mood and sociability associated with reduced seizure severity, but no difference in side-effect profile when compared with placebo (Motte et al, 1997). In comparison studies with carbamazepine and phenytoin, lamotrigine has been found to produce positive behavioural effects, but it has also been reported that lamotrigine can produce some neurobehavioural toxicity (Meador & Baker, 1997).

Perampanel

A recent multi-centre pragmatic retrospective assessment found that perampanel is safe and may be better tolerated by people with ID than the general population (Shankar et al, 2017b). Over 50% seizure improvement was observed in 24% of those with mild ID, and in 26% of those with moderate to severe ID. There is a suggestion that perampanel should be used with caution in individuals with underlying (or a history of) mental illness as there is an increased risk of worsening of their behaviour and mental state.

Phenytoin

The current recommendations suggest that phenytoin should not be prescribed for people with ID unless it is considered to be in the patient's best interests. Those prescribed phenytoin require close monitoring in order to prevent intoxication and subsequent phenytoin-induced encephalopathy (Iivanaien, 1998). Poor monitoring can result in toxic levels, which may manifest as cerebellar ataxia, drowsiness and cognitive decline. This is a potential difficulty for some people with ID who are unable to tolerate the regular venepuncture required for long-term routine monitoring. Phenytoin also has multiple significant interactions with other drugs. As a significant minority of people with ID are on various long-term medications, the potential for dangerous drug interactions could be greater.

Sodium valproate

Sodium valproate has been widely used as a broad-spectrum AED for over 40 years, with a relatively good safety profile (Nalivaeva et al, 2009). Some research has demonstrated that people with ID who have treatment-resistant epilepsy may be more responsive to valproate. Valproate is a first-line treatment for primary generalised

seizures and syndromes, as it is generally well-tolerated and effective in treating a variety of seizure types (Friis et al, 1993). The SANAD study compared the longer-term effects of valproate in people with generalised seizures and seizures difficult to classify, such as those seen in many people with ID. It found that the 12-month remission rate of seizures with valproate was significantly greater than with topiramate, but no significant difference was identified between valproate and lamotrigine. This effect was greater when the analysis was restricted to people classified as having idiopathic generalised epilepsy compared with the overall population. It was concluded that valproate ought to remain the first-line treatment for the majority of people with idiopathic generalised epilepsy or seizures which are difficult for the clinician to classify (Marson et al, 2007). Limitations to the use of valproate in the general population relate to its teratogenic potential, and it often causes weight gain (Hannah & Brodie, 1998). There are also concerns about its use in some people who have rare causes of ID and epilepsy such as mitochondrial disease and ornithine transcarbamylase deficiency.

Topiramate

The efficacy of topiramate has been investigated in a randomised placebo-controlled add-on study with 57 participants with epilepsy and ID (Kerr et al, 2005). Seizure frequency varied significantly among the participants, but an overall reduction in frequency of 32% was noted in the topiramate group (compared with 1% for placebo). Topiramate was found to be generally well tolerated and did not have a negative impact on behaviour. Very few participants withdrew from the study because of adverse effects of medication, and the study suggested that topiramate reduced seizure rates without compromising quality of life. A small review has examined the treatment response to topiramate in an institutionalised adult ID population (Janowsky et al, 2003). The results suggest that topiramate may have a role in the treatment of challenging/maladaptive behaviours in people with ID when used as an add-on medication for the treatment of partial and generalised seizures. Another review of the effectiveness of topiramate in individuals with ID and epilepsy found that the drug was effective for a wide range of seizure types (generalised and partial) and was effective against atonic seizures in Lennox–Gastaut syndrome (Kerr, 1999). Despite this evidence, topiramate is still sparingly used as prescribers believe that it causes quite a lot of sedation, word-finding difficulty and weight loss.

Other AEDs

There is some emerging evidence from retrospective open-label studies that newer AEDs such as lacosamide may be a useful adjunctive therapy for those with ID and treatment-resistant epilepsy.

The evidence is, however, very limited to date, and caution is required in interpretation (Flores et al, 2012).

Rufinamide has been assessed in an RCT of people with Lennox–Gastaut syndrome, in which 138 individuals received either rufinamide or placebo. Significant improvements were seen in total seizure frequency and atonic (drop) attacks, with a 50% responder rate overall. Common adverse events included somnolence and vomiting (Glauser et al, 2008).

To date, evidence of the tolerability or efficacy of AEDs such as pregabalin, brivaracetam, tiagabine, stiripentol, ethosuximide, eslicarbazepine, oxcarbazepine, retigabine and zonisamide is extremely limited in the scientific literature. Stiripentol is an orphan drug and would be used only for specific conditions such as Dravet syndrome and is best prescribed under expert guidance.

Pregabalin is a well-used 'multipurpose' drug having indications in the management of pain and anxiety, conditions that are associated more often in people with ID. The fact that relief from these conditions can have a positive effect on seizures is worth keeping in mind.

Ethosuximide, tiagabine and retigabine need to be used with extreme caution with clear rationale of why they are prescribed and what is served by their inclusion.

There is anecdotal evidence to suggest that zonisamide, if built up gradually, has a positive effect on seizures. Cautions include its impact on mental state and behaviour.

Eslicarbazepine and oxcarbazepine are considered to have a favourable effect on mood and behaviour. Advantages of eslicarbazepine include its dosing recommendations, which allow for swift attainment of a therapeutic dose.

Brivaracetam is a new drug and there is no major evidence yet for its use in people with ID.

Choosing the most appropriate AED

The NICE clinical guideline on epilepsies (CG137) states that the choice of treatment and monitoring of tolerability and effectiveness should be the same for people with ID as for the general population (NICE, 2012: section 1.16). Recommendations for the pharmacological management of epilepsy are set out in section 1.9 and Appendix E of the guideline.

However, while CG137 sets out broad principles of epilepsy treatment, the lack of specific consideration of problems associated with ID is clear. The guidance does include a section on ID, but it is inadequate.

Owing to the complexity of the presentation of epilepsy in people with ID specific considerations are needed. In general, it is advised that AEDs should be prescribed at the lowest possible dose and with slow titration. This will aid in accurate assessment of the effect of the AED on seizure control and of its side-effects in the context of communication difficulties and comorbid mental illness; in particular, side-effects may present as behavioural change.

Box 1 summarises internationally recognised criteria for assessing the quality of evidence in the medical literature. We use this grading

Box 1 Grading of evidence

Ia	Evidence from systematic reviews or meta-analysis of RCTs
Ib	Evidence from at least one RCT
II	Evidence from at least one controlled study without randomisation, and from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case–control studies
IV	Evidence of post-study analysis of a section of the ID population following large sample studies
V	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

(adapted from Canadian Task Force on the Periodic Health Examination, 1979; Sackett, 1989)

system in Table 4 (see next two pages), which provides an overview of practical evidence-based prescribing for people with ID. The most relevant paper has been cited for each drug. A recommendation is given in the form of a traffic light system:

- RED Only use in exceptional circumstances
- AMBER Could be considered if benefits outweigh risks or as second-line treatments
- GREEN Needs to be considered as first-line treatment

The traffic light system integrates both clinical experience, evidence of efficacy and side-effects to provide a recommendation.

Table 4 Evidence and suitability of specific commonly used anti-epileptic drugs (AEDs) in the intellectual disability (ID) population

Drug	ID-specific evidence	Type of evidence	Comments	Level of evidence	Suitability in ID
Lamotrigine	Motte et al, 1997	Lennox–Gastaux only; RCT using placebo	Under-powered; specific syndrome	I	Green Pros: One of the most well-studie Possible interactions Slow titration to dose
	Buchanan, 1995	*n* = 34; majority showed >50% improvement	Under-powered		
	Gidal et al, 2000	*n* = 44; 45% showed >50% improvement, 20% showed deterioration	Under-powered		
	McKee et al, 2006	*n* = 22; sub-analysis of larger study	Under-powered		
Sodium valproate	Marson et al, 2007	Sub-analysis of difficult-to-treat epilepsy	Multiple methodological issues	V	Green One of the most commonly used AEDs in ID and, despite the limited evidence, recognised as 'green'. Note that it is red if the patient (usually with borderline to mild ID) is a sexually active female of childbearing age. Pros: First-line AED with recognised suitable mood profile Cons: Risk of polycystic ovarian syndrome Limited evidence in people with ID
Levetiracetam	Kelly et al, 2004	*n* = 64; observational study as add-on; 38% seizure free	Improved seizure control in majority and carer satisfaction	III	Amber Pros: Does not interact with other commonly prescribed medication in people with ID Has been well studied in the general population and is considered first-line medication Cons: Needs more studies in ID Concerns exist about behavioural and mental side-effects, although the phenomenon might be more common in general population than in ID because of titration difference
	Brodtkorb et al, 2004	*n* = 184 (56 of whom had ID); equally effective	Study focus was on behavioural adverse effects – worse in ID		
Topiramate	Kerr et al, 2005	*n* = 57; RCT, double-blind to placebo; 32% reduction in seizure frequency in treatment group *v.* 1% in placebo group	Under-powered No negative effect on behaviour	I	Amber Pros: Reasonable evidence in ID No major interactions, other than with oral contraceptives Cons: Although the RCT found no effect on behaviour, real-world experience suggests that it has an impact on mood and behaviour Weight loss

continued

Gabapentin	Crawford et al, 2001	Add-on comparative open study with lamotrigine – no difference	Under-powered Side-effects of aggression	II	Amber No definitive details of efficacy or potential for harm
Perampanel	Shankar et al, 2017b	Retrospective case series, *n* = 144 (general population: 71; mild ID: 48; moderate to profound ID: 25)	>50% seizure improvement in 24% with mild ID, and in 26% with moderate to profound ID. Safe in people with ID and better tolerated than in general population. Psychiatric side-effects	III	Amber Pros: Does not usually interact with other commonly prescribed medication in people with ID Has been well studied in the general population and the ID population in real-world studies Considered a viable alternative in treatment-resistant epilepsy Cons: Concerns exist about behavioural and psychiatric side-effects
Lacosamide	Flores et al, 2012	Real-world cohort *n* = 403, 18% with ID: sub-analysis No differences between ID *v.* non-ID	Case selection	IV	Amber Pros: Is considered to have a favourable side-effects profile Cons: Needs more evidence
Carbamazepine	Kaski et al, 1991	Improved efficacy using slow-release preparation *v.* standard preparation	No direct evidence of tolerability or efficacy	II (but unrelated)	Amber Pros: Long-standing AED, recognised first-line treatment Cons: No direct evidence of efficacy Multiple drug interactions with other commonly prescribed medication in people with ID, such as other AEDs and psychotropics
Phenytoin	None	None	–	V	Red Unsuitable owing to: multiple drug interactions behavioural side-effects need for regular blood monitoring Any consideration of phenytoin needs a comprehensive discussion with the patient of its benefits and risks weighed in balance against alternatives, efficacy and side-effects
Phenobarbitone	None	None	–	V	Red Unsuitable owing to: cognitive side-effects multiple drug interactions behavioural side-effects need for regular blood monitoring Any consideration of phenobarbitone needs a comprehensive discussion with the patient of its benefits and risks weighed in balance against alternatives, efficacy and side-effects

Prescribing guidance

In general, the most appropriate way to initiate a new AED in the ID population is to follow the principle of a low starting dose and slow titration. Many experts in the field do so at half or even quarter the rates suggested for the general population. This reduces the likelihood of dose-related adverse effects. It also allows greater opportunity for identifying the minimum effective dose and less chance of missing the 'therapeutic window', above which worsening of seizure control may occur. Individuals may also metabolise drugs at different rates, and slow titration is a benefit here too.

Good practice suggests that a 'new' drug is added before the 'old' drug is withdrawn, in order to ensure that there is no confusion about symptoms or changes in epilepsy due to a drug titration. The main disadvantage to a cautious introduction is the potential for a lengthier time to seizure control. However, most people requiring change have treatment-resistant epilepsy and multiple seizures and so a cautious approach looking for emergent side-effects outweighs rapid dose titration to see whether seizure control can be achieved. In some cases, a lengthy titration might result in patients or their families losing confidence in the medication, but they should be counselled during the consultation process to ensure realistic expectations.

If rapid seizure control is required, it may be necessary to titrate a new drug alongside a 'rescue medication' such as clobazam.

Given the significant physical and psychiatric comorbidities that often exist in people with ID, medication must be tailored to the individual. Procedures such as those identified in the Mental Capacity Act 2005 for England and Wales, including the best interests process, should be used where applicable to ensure that treatment goals are holistic and realistic, particularly for people at high risk, such as those with drug-resistant epilepsy. Decisions should be representative of the individual's wishes and take into account their quality of life and daily activity, while ensuring optimum safety from seizures and their side-effects. Communication aids such as 'easy read' information or speech and language specialists should be considered to help the individual to make a treatment choice.

The flowcharts on the next page outline the procedure for making an initial treatment decision (Fig. 1) and for choosing an alternative treatment if monotherapy fails (Fig. 2).

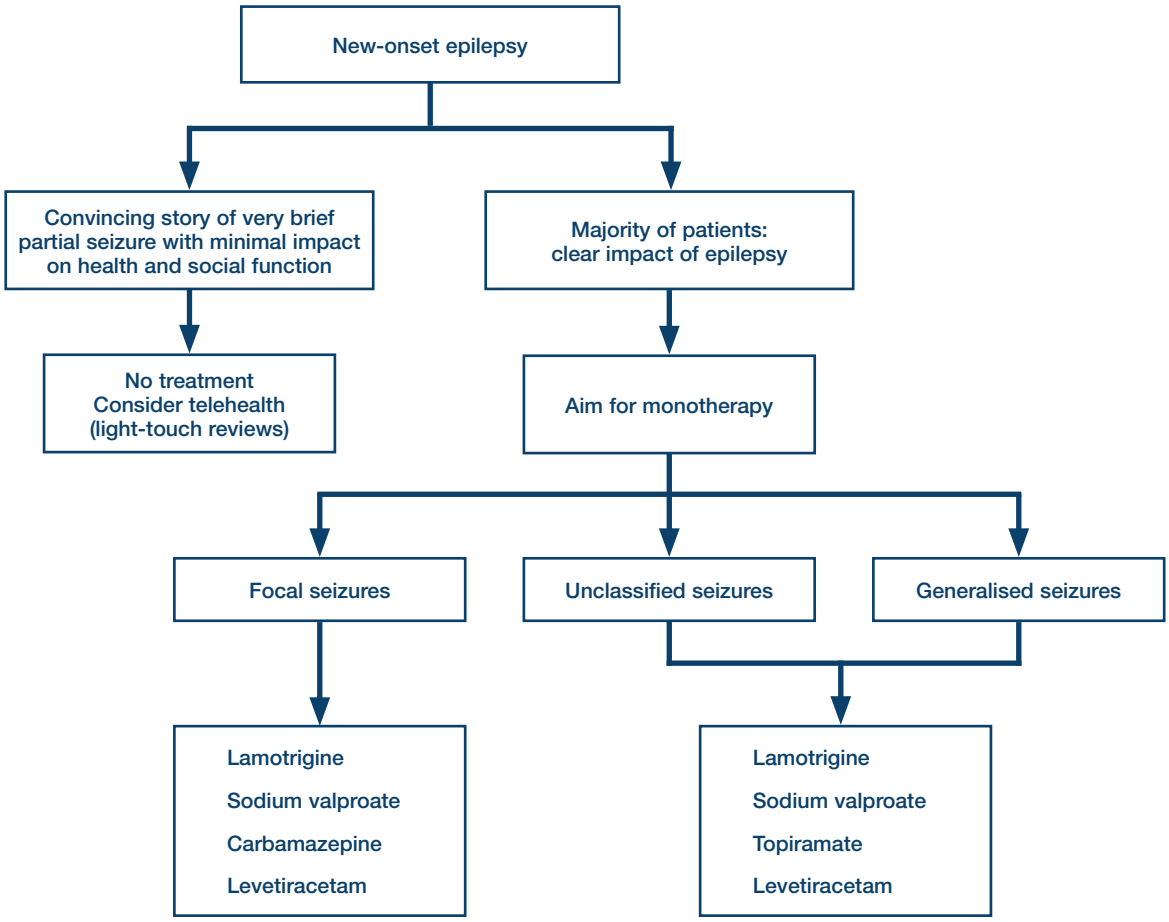

Fig. 1 Making an initial treatment choice (adapted from Shankar et al, 2017a).

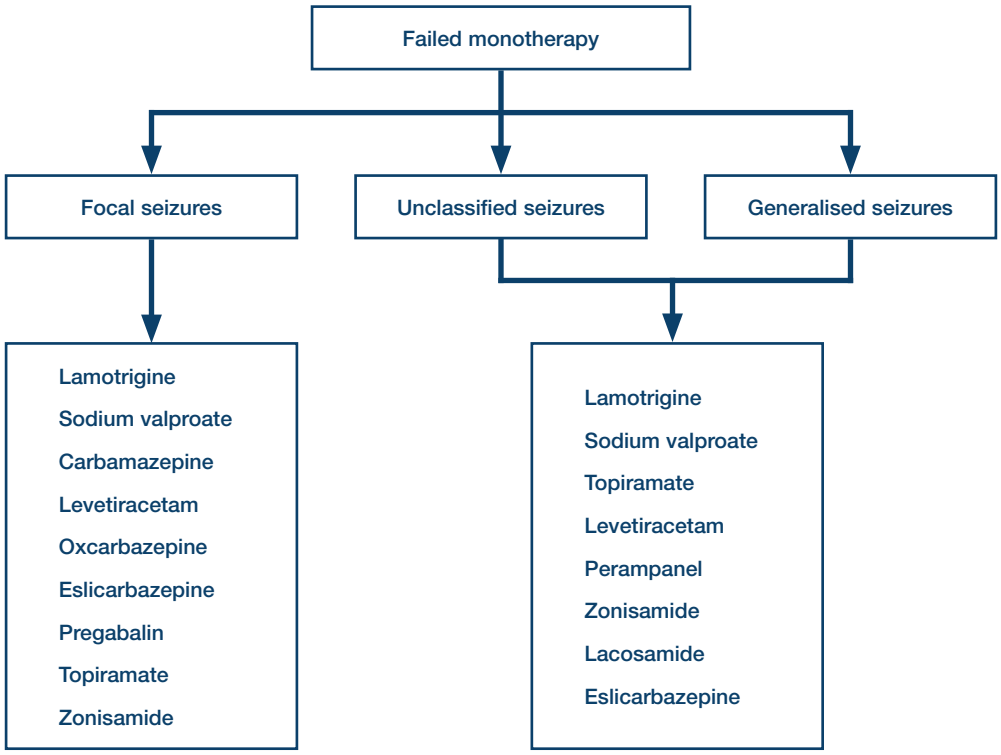

Fig. 2 Making a treatment choice if monotherapy fails (adapted from Shankar et al, 2017a).

Considerations when prescribing in ID

Before prescribing AEDs for people with epilepsy and ID there are a number of key considerations (Fig. 3). The first should be to ensure the individual's safety, as treatments and outcomes cannot be guaranteed to be successful. This includes carrying out a detailed personalised risk assessment of the effects of their epilepsy. Two key risk areas to consider are bathing and sudden unexpected death in epilepsy (SUDEP). The SUDEP and Seizure Safety Checklist (https://sudep.org/checklist) is a practical, evidence-based tool that is quickly completed in the clinic (Ridsdale et al, 2011; Ridsdale, 2015; Shankar et al, 2013a; Ostler et al, 2015). It promotes meaningful communication, provides a baseline for comparing changes in risk factors over time, and supports prioritisation of clinical activity. Ensuring the safety of the individual also includes safe prescribing. It is therefore important to approach prescribing in a person-centred way, evaluating the risks and benefits of AED prescription in the context of seizure profile, comorbidities and other medication.

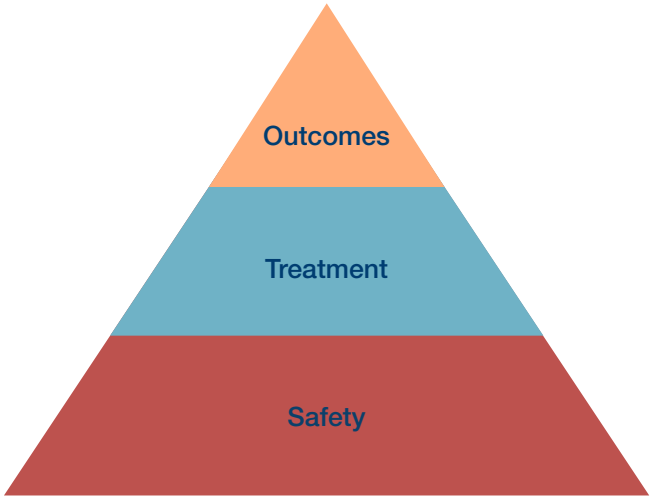

Fig. 3 The hierarchy of considerations in prescribing AEDs for people with ID.

The aim of any treatment should be to underpin specific holistic outcomes based on the individual's seizure history, comorbidity, level of ID and expected quality of life. There are likely to be numerous mitigating biological, psychological and social factors that have an influence on risk and treatment planning. A thorough environmental risk assessment is essential as the individual may well be reliant on family or caregivers for support with treatment and risk reduction. Epilepsy awareness training should be provided to everyone involved in the individual's care, and where seizure rescue medication is prescribed specific training should be given to anyone involved in its administration. More detailed information about the wider management of epilepsy in people with ID is set out in College Report CR203 (Royal College of Psychiatrists, 2017).

The education, observation, treatment goals and management plans should be brought together in an overall individualised 'epilepsy management plan' for each person, ideally formulated in a single written plan. This plan can then be shared with the GP, other clinicians and the individual's family and paid carers as appropriate. The key considerations for such a plan are shown in Fig. 4.

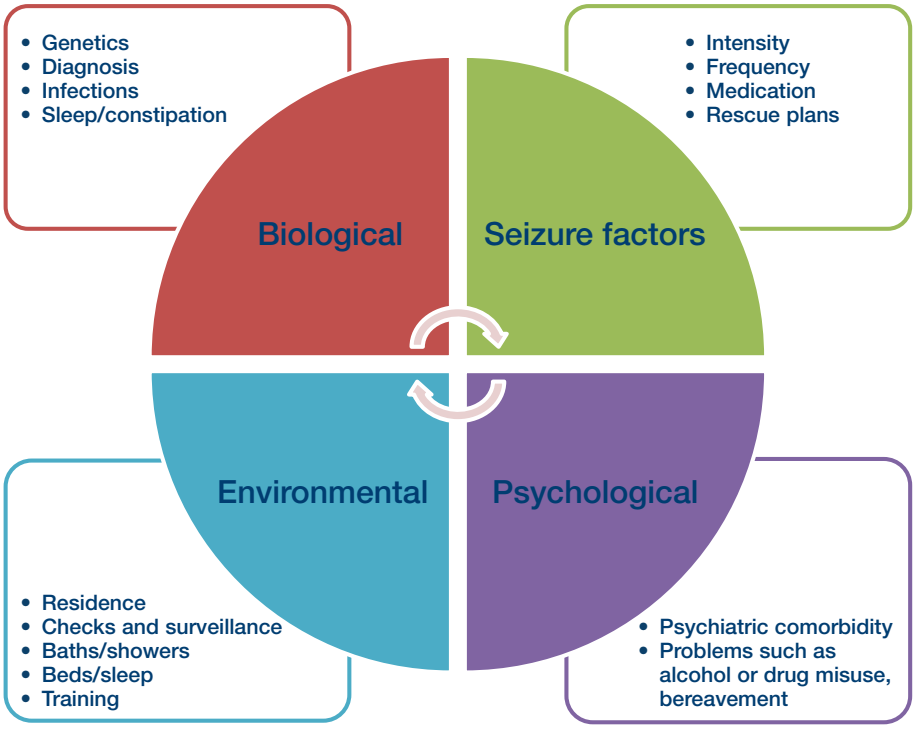

Fig. 4 Considerations in the person-centred approach to the treatment of people with epilepsy and ID.

Genetic investigations and AED prescribing

Although it is not possible for clinicians to keep up to date with every new genetic discovery of an epilepsy-related gene, it is important to investigate patients with ID and epilepsy who have no diagnosis to account for their comorbid neurodevelopmental disorders. The findings from genetic investigations might influence epilepsy treatment, including the choice of AED. Identification of an *SCN1A* mutation in an individual presenting with a Dravet syndrome phenotype should lead to the avoidance or withdrawal of lamotrigine, phenytoin, carbamazepine and other sodium channel-blocking AEDs which can aggravate seizures (as mentioned in the Summary of evidence). Instead, AEDs such as sodium valproate, clonazepam and stiripentol are indicated. A mutation of the *SLC2A1* gene (which codes the cerebral glucose transporter), in the presence abnormal movements and/or a family history of seizures, helps in the diagnosis of glucose transporter type 1 (GLUT1) deficiency, which responds very well to a ketogenic diet. Some mitochondrial disorders and cerebral creatine deficiency syndromes (CCDS) are also associated with ID and epilepsy, and may respond to specific treatments. A Cochrane Review (Pfeffer et al, 2012) did not identify any evidence-based disease-modifying treatments for mitochondrial disorders, but reports are emerging in the literature of successful treatment, including seizure reduction in some patients with mitochondrial disorders treated with, for example, coenzyme Q10 and L-carnitine. L-carnitine has also been used to successfully treat seizures in guanidinoacetate methyltransferase (GAMT) deficiency, one of the CCDS (Mercimek-Mahmutoglu et al, 2006; Stockler-Ipsiroglu et al, 2014). Improvements were also seen in motor movement, but not in intellectual functioning.

Genetic testing can also help avoid serious iatrogenic side-effects. The recessive polymerase-gamma (POLG) related disorders form part of the group of mitochondrial disorders and are commonly associated with seizures but have a complex and variable presentation. Sodium valproate can cause irreversible liver failure in patients with a *POLG* mutation and consideration should be given to testing people for *POLG* mutations when presenting with seizures and liver dysfunction. Human leukocyte antigen (HLA) testing should be considered for patients of Han Chinese extraction owing to the significantly increased risk of mild to severe life-threatening rashes secondary to carbamazepine exposure. For instance, the HLAB*1502 allele is a major risk factor in populations of South Asian origin. For all patients with ID and epilepsy of unknown cause, clinicians should consider arranging micro-array comparative genomic hybridisation (array CGH) testing, which is fairly easily available. Specific epilepsy gene panels and whole exome sequencing (WES) are available in specialist centres only. Diagnosis and treatment of disorders such as CCDS often takes place in tertiary centres. Where appropriate, clinicians should liaise with regional genetics departments.

Complexity

The NICE clinical guideline on epilepsies (CG137) outlines the difficulties of diagnosing epilepsy in children and adults with ID (NICE, 2012). The problem arises because of the multiple comorbidities, including stereotypic or other behaviours that may mimic seizures. Individuals with ID and epilepsy often have very complex needs and a wide range of comorbid physical, neuropsychiatric and behavioural difficulties (Cooper et al, 2007). As a result of this complexity these individuals have less access to diagnostic investigations and have less contact with specialist services than the general epilepsy population (Hanna et al, 2002).

ID and epilepsy are independently associated with an increased risk of premature mortality. The combination of ID and epilepsy, together with associated physical comorbidity, significantly raises standardised mortality ratios (Hitiris et al, 2007; Heslop et al, 2013). Comorbid physical health conditions inevitably lead to polypharmacy and the increased risk of drug interactions, which could have potentially adverse effects for the individual. For example, individuals with ID are more susceptible to bone disorders. This may in part be contributed to by prolonged immobilisation and vitamin D deficiency (Wagemens et al, 1998). There is also clear evidence that AEDs themselves can lead to bone density disorders with chronic use (Petty et al, 2005). This is of particular importance as people with ID are more likely to have refractory epilepsy and be prescribed multiple AEDs for a prolonged period. NICE recommends that vitamin D should be prescribed proactively in this population (NICE, 2014).

Epilepsy is also strongly associated with an increased risk of mental health problems, and standards have been published for the treatment of neuropsychiatric conditions (Kerr et al, 2011) and behavioural manifestations (Kerr et al, 2016). In a clinical setting, the key is identification and assessment of the association between behavioural changes and the seizure disorder. The point prevalence of mental illness in the ID population is over 50%, with many individuals having more than one diagnosable psychiatric disorder (Cooper et al, 2007). People with ID and active epilepsy are also at greater risk of developing mental illness (Turky et al, 2011), and it can affect epilepsy assessment and treatment. The clinician needs to identify whether the mental illness is pre-ictal, ictal, post-ictal or inter-ictal. Pre-ictal psychiatric disturbance occurs in the days, hours or seconds prior to a seizure and is usually readily identifiable. Ictal disturbance in a person with ID is often manifested by the fluctuating levels of consciousness seen in non-convulsive status epilepticus. Post-ictal

disturbance may be immediate and, in essence, a confusional state, or it may have a more severe presentation, such as post-ictal psychosis. Inter-ictal psychiatric disturbances are not temporally associated with the seizures.

There may be some confusion for clinicians about behaviours that are associated with epilepsy and its treatment, and those that are not. Differentiating these more complex seizure presentations from psychiatric disturbance or non-epileptic seizures can be very challenging in the general population. Considering these presentations in the ID population is further complicated by the high prevalence of repetitive stereotyped motor behaviours (Chebli et al, 2016). The role of psychotropic medication that has epileptogenic potential must also be carefully considered (Alper et al, 2007). For specific guidance on behavioural manifestations and neuropsychiatric management for this population see Kerr et al (2011, 2016). A large proportion of people referred to specialist epilepsy units have been shown to have a misdiagnosis of epilepsy following neurophysiological testing (Donat & Wright, 1990; Raymond et al, 1999).

Autism

It is now well-recognised that rates of epilepsy are higher in people with autism than they are in those without the condition, and a variety of mechanisms appear to underpin this high comorbidity rate (Buckley & Holmes, 2016). In the future, better understanding of the biology of these mechanisms, combined with increased knowledge of the modes of action of AEDs, may enable the development of a specific approach to AED prescribing for epilepsy in people with autism. Currently, however, the clinical cautions and the limited evidence base from which to draw treatment guidelines that apply when prescribing AEDs to people with ID also apply when prescribing AEDs for epilepsy management in people with autism. Choice of AED should, as for those with ID, be determined by similar considerations of seizure type, adverse-effect and drug-interaction profiles, and associated psychiatric and behavioural presentations. The presence of comorbid neurodevelopmental disorders such as autism or other pervasive developmental disorders (PDDs) may be an indication to initiate treatment early. There is a significant overrepresentation of seizures in this population. About 30–40% of children with autism develop clinical epilepsy by adolescence. The prevalence of epilepsy may be as high as 67% in children with comorbid autism, ID and cerebral palsy at the age of 10, and seizures continue to adulthood (Tuchman & Rapid, 2002). The remission rate for seizures in autism is low, at only 16% (Danielsson et al, 2005). The evidence of additional associations is extremely helpful in deciding a course of action when there is diagnostic ambiguity as to whether the presenting symptoms are of a seizure or not.

Dementia

There is a paucity of research into dementia and ID as, until recently, dementia did not have time to manifest itself, owing to the limited life expectancy of this population. As people with ID are now living longer, it has become apparent that they can develop many types of dementia. Early symptoms of dementia in people with ID are reported to be different from those experienced by the general dementia population. One specific area of symptom variation in ID is an increased prevalence of behavioural as opposed to cognitive/memory changes. There is a well-established association between the emergence or worsening of seizures and progressive dementia in people with Down syndrome (Lott et al, 2012).

As with the general population, people with ID are at risk of seizures secondary to cerebrovascular and metabolic events, among other precursors of dementia. Studies in the general population have shown that seizures or epilepsy are substantially more common in patients with dementia than in dementia-free patients and tend to be more frequent in advanced stages of the disease (Friedman et al, 2012; Pandis & Scarmeas, 2012). Many widely used drugs are known to potentially lower seizure threshold. Anti-dementia drugs such as cholinesterase inhibitors are proconvulsive (Caramelli & Castro, 2005), so before AEDs are considered any concomitant medication needs to be reviewed. No particular AED has been identified to have specific advantage for dementia-associated seizures. It is important that prescribing takes into account age-related changes in drug absorption and metabolism (Pohlmann-Eden & Eden, 2011). Sodium valproate, lamotrigine and levetiracetam are recommended as first-line AEDs, but it should be noted that levetiracetam can cause behavioural disturbances, lamotrigine must be slowly titrated and has potential for interaction and allergic reactions, and sodium valproate can cause tremor and thrombocytopaenia.

Catamenial epilepsy

Catamenial epilepsy refers to an exacerbation of seizures linked to a woman's menstrual cycle. Three patterns of hormonally based catamenial epilepsy have been identified (Herzog et al, 1997): perimenstrual, when oestrogens increase at a faster rate than progesterone; pre-ovulatory; and luteal phase, when progesterone is lower than normal during the ovulatory cycle owing to inadequate corpus luteal development.

Oestrogens are considered proconvulsant and progesterones anticonvulsant, and increased seizure frequency has been reported during the follicular phase, when oestrogen concentrations are at their highest (Backstrom, 1976). During anovulatory cycles, seizure frequency tends to be higher in the second half of the cycle (Herzog et al, 1997). It is important to note that actual catamenial epilepsy,

using a strict definition of ≥75% of seizures occurring within 4 days preceding and 6 days after the onset of menstruation, is less frequent than is actually reported (Duncan et al, 1993).

Perimenstrual exacerbation of seizures may also be due to lower serum AED levels. This can certainly occur with phenytoin (Reddy 2010), but whether it can occur with other AEDs has not been adequately studied. In confirmed catamenial epilepsy, further investigations to inform treatment include measuring mid-luteal serum progesterone levels to check for luteal-phase deficiency in secretion. In a perimenstrual catamenial pattern, check trough AED levels on day 22 (when oestradiol and progesterone levels are high and AED levels should be 'normal') and on day 1 (when oestradiol and progesterone levels are low). Low AED levels at this time (perhaps related to increased drug metabolism) might be the cause of perimenstrual seizure exacerbation (Klein & Herzog, 1997).

Evidence supports the use of clobazam for the management of catamenial epilepsy (Feely & Gibson, 1984). A dose of 10 mg at night during the perimenstrual period is often sufficient; for patients who are unable to tolerate this dose, administration of 10 mg on alternate nights could be considered, given clobazam's long half-life.

Other options include increasing the dose of the AED around the time of risk or introducing acetazolamide for perimenstrual seizures. Particularly if premenstrual progesterone levels are low, hormonal manipulation using, for example, medroxyprogesterone could be considered. Progesterone therapy has been used with some success to increase relative progesterone concentrations or convert anovulatory to ovulatory cycles (Herzog, 1999). However, there is limited evidence for the effectiveness of these approaches in treating catamenial epilepsy.

Ultimately, if catamenial epilepsy does not respond to any of the above measures, consider referring to endocrinology or gynaecology colleagues, for more specialist approaches to hormonal treatments.

Recording an epilepsy diagnosis

Since multiple diagnoses and comorbidity are more the norm than the exception in people with ID, the recording of the diagnosis of epilepsy should be in the context of a detailed diagnostic assessment and formulation that covers all of the following (Faculty of Psychiatry of Intellectual Disability, 2016):

- the degree of ID
- the cause of the ID (including genetic syndromes, behavioural phenotypes)
- other developmental disorders (including autism spectrum disorders, hyperkinetic disorder)
- mental illnesses

- personality disorders
- disorders related to substance misuse or dependence
- physical disorders (including any of the causes of the ID)
- psychosocial stressors (long-standing issues as well as recent environmental changes)
- types of behaviours that challenge (in this structure, behaviours that challenge are not treated as a diagnosis, but as a presenting symptom in the context of a range of biopsychosocial factors).

Side-effects – challenging behaviour, physical and mental health

The NICE clinical guideline on epilepsies (CG137) clearly states that, when prescribing AEDs to people with ID, particular attention should be given to observing for any adverse cognitive or neuropsychiatric effects (NICE, 2012).

Neuropsychiatric disturbance and challenging behaviour

Behavioural disturbance is often reported in the context of a new AED prescription or an increase in dose (Table 5). In a population in which epilepsy and behavioural problems are common, cause and effect is often very difficult to establish. Before any medication change it is often helpful to document baseline behaviours so that a more objective assessment may be possible following the introduction of

Table 5 Recommendations for use of anti-epileptic drugs (AEDs) in intellectual disability based on cognitive and behavioural complications

	Caution		Neutral		Positive		
AED	Cognition	Behaviour	Cognition	Behaviour	Cognition	Behaviour	Inconclusive evidence
Older	Phenobarbital Phenytoin (based on levels)	Phenobarbital Phenytoin	Valproate Carbamazepine	Carbamazepine		?Valproate	Ethosuximide Clobazam
Newer	Topiramate	Gabapentin Topiramate Levetiracetam	Gabapentin Oxcarbazepine		Lamotrigine Levetiracetam	Lamotrigine	Vigabatrin Felbamate Tiagabine
Newest	Zonisamide	Zonisamide Perampanel	?Lacosamide ?Perampanel ?Eslicarbazepine	?Lacosamide ?Eslicarbazepine			Pregabalin Rufinamide Retigabine Stiripentol

Adapted and modified from Aldenkamp et al (2016).

a new drug. If a change in behaviour type or frequency does take place, there are several possible causes other than medication. The behaviour may be the consequence of improved seizure control as the individual becomes more alert and responsive. A new AED may result in previously rapidly generalising focal epilepsy subsequently manifesting as an aura only, to which the individual may respond fearfully. There may be environmental causes, such as a change in carers or cohabitors, day care or residential/respite provision or the loss of a family member. More commonly, however, behavioural changes are a communication of emergent side-effects and these should be acknowledged and explored.

Cognition

Knowledge of the side-effect profiles of the various AEDs is essential, as people with ID may be particularly susceptible to developing adverse effects and less able to communicate about them. Adverse effects may be acute and usually dose related, idiosyncratic or linked to chronic administration. AEDs that are more commonly known to affect cognition, such as phenobarbitone or topiramate (Table 5), may require careful consideration before prescribing for an individual with ID. The prescriber must weigh the benefits of improved seizure control against the short- and long-term risks of side-effects.

Weight gain/loss

Several AEDs have been found to predispose to significant change in weight. In a population in which obesity is already common this should be considered before initiating treatment; valproate, gabapentin and pregabalin are potentially associated with weight gain. Conversely, anorexia can be a problem for a minority, and the prescription of topiramate or zonisamide may result in a loss of appetite and weight.

Bone density

The development of osteoporosis is associated with chronic AED administration: decreased bone density has been reported with administration of phenytoin, phenobarbitone, primidone, carbamazepine and valproate (Farhar et al, 2002). This is of particular relevance to the ID population, as many will have significant coexisting risk factors for decreased bone density and fracture. Immobility, lack of exposure to sunlight, poor dietary intake of vitamin D, early menopause and co-prescription of antipsychotics are all more common among the ID population and may contribute to poor bone mineralisation. The exact mechanism by which AEDs predispose to osteoporosis is unclear: possibly it is through the enzymatic induction of vitamin D.

Other side-effects

The possibility of adverse physical effects from an AED, such as ataxia, diplopia or gastric irritation, should also be considered as an explanation for behavioural change. It is also important to be vigilant for side-effects such as neutropaenia and thrombocytopaenia. These should be suspected if, for example, there are recurrent infections, tiredness or falls. As the majority of people with ID are unable to represent their interests suitably and a significant number have problems in communication and comprehension, clinicians should consider annual monitoring of routine biochemistry based on the drugs prescribed, to recognise and treat any potential developing side-effect. We recommend that some or all basic tests such as blood pressure, body mass index, kidney function tests, liver function tests (LFTs), full blood count (FBC), glycated haemoglobin, and cholesterol and lipid profile be considered at least annually. Tests need to be rationalised on the basis of the specific side-effects of individual AEDs, their expected frequency, clinical presentation and anticipation. For example, people on carbamazepine will benefit from routine FBC and kidney function tests and those on sodium valproate from LFT and FBC. For people on chronic AED treatment and other medication, occasional dual energy X-ray absorptiometry (DEXA) scan and bone profile might be warranted to check on changes, especially at key junctures of life such as menopause. Similarly, electrocardiograms (ECGs) to look for change in heart function might be called on occasionally. Opportunity to conduct the investigations needs to be taken into account in people with ID. It would be good practice to ensure that a battery of investigations and tests identified as being in the best interests of the individual is done annually, or earlier if there is cause for concern (for example, easy bleeding when on sodium valproate). In those on whom it is difficult to conduct investigations (owing to the high levels of distress caused), good practice also suggests that, if they appear clinically well, an attempt be made to deliver relevant tests at least once every 3 years.

Drug preparations and their relevance

Many AEDs have a narrow therapeutic index. In 2013, the UK Commission on Human Medicines (CHM) reviewed adverse reactions reported to the Medicines and Healthcare products Regulatory Agency (MHRA) arising from prescription changing (switching) to generic formulations of AEDs in patients previously stabilised on branded products. As a result of the CHM's recommendations, the MHRA (2013) advises that people prescribed certain AEDs should be maintained on the specific manufacturer's product because of the risk of adverse effects or loss of seizure control when changing preparations. On the basis of therapeutic index, solubility and absorption, the MHRA groups AEDs are into three categories of potential risk on switching:

- Category 1 (phenytoin, carbamazepine, phenobarbital, primidone) – prescribers should ensure that patients are maintained on a specific brand or a specific manufacturer's generic product
- Category 2 (valproate, lamotrigine, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide, topiramate) – prescribers should decide whether it is necessary to maintain a patient on a particular manufacturer's product on the basis of clinical judgement and consultation with the patient and/or carer, taking into account factors such as seizure frequency and treatment history
- Category 3 (levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin) – it is unnecessary to maintain patients on a specific manufacturer's product unless there are particular concerns such as patient anxiety or risk of confusion or dosing errors.

Common drug interactions

AEDs may interact with each other and with other medications. These interactions may be divided into three levels of importance (Table 6). In this chapter we give examples of common drug interactions that it is important to be aware of when prescribing AEDs (Patsalos, 2016). A full list of interactions of AEDs with other drugs can be found on the NICE BNF website (https://bnf.nice.org.uk/interaction).

Table 6 Levels of importance of interactions of anti-epileptics with other drugs and potential serious clinical consequences

Drug interaction	Potential consequences
Level 1 interactions: Avoid combination as may lead to potentially serious adverse events	
Examples	
Carbamazepine/phenytoin/phenobarbitone/ primidone and oral contraceptive pill	Reduction in contraceptive effect
Carbamazepine and clarithromycin/erythromycin	Elevated serum carbamazepine levels, resulting in toxicity
Lamotrigine and oral contraceptive pill	Up to 50% reduction in serum lamotrigine levels and loss of seizure control; note: if a woman taking lamotrigine stops taking oral contraceptive, lamotrigine level will increase, so dose adjustment by up to 50% may be required to avoid toxicity
Lamotrigine and carbamazepine	Carbamazepine often reduces the effects of lamotrigine, but lamotrigine sometime increases the effects of carbamazepine, so it is difficult to clearly attribute side-effects or even effectiveness to one or the other drug
Carbamazepine and clozapine	Increased risk of agranulocytosis
Carbamazepine and lithium	Neurotoxicity
Level 2 interactions: Caution advised in prescribing or any dose adjustments	
Examples	
Valproate and lamotrigine	Elevated serum lamotrigine levels, resulting in skin rash, neurotoxicity
Valproate and phenobarbitone	Elevated serum phenobarbital concentration, resulting in toxicity
Carbamazepine/phenytoin/phenobarbitone/ primidone and warfarin	Reduced serum warfarin concentration
Carbamazepine/phenytoin/phenobarbitone/ primidone and ciclosporine	Reduced serum concentrations of ciclosporine, resulting in therapeutic failure
Level 3 interactions: Clinically relevant changes in serum concentrations unlikely	

Adapted from Johannessen & Johannessen Landmark (2010).

As well as interactions between AEDs it is important to be aware of potential interactions with medication prescribed by other clinicians.

Oral contraceptives

One key example of interaction is with the oral contraceptive pill (OCP). Some methods of contraception may be less effective in preventing pregnancy for women taking certain AEDs (Reddy, 2010). This is because some AEDs are hepatic enzyme-inducing: they increase the metabolism of both progesterone and oestrogen and thus can affect how well the contraceptive works. Non-enzyme-inducing AEDs are unlikely to affect contraception.

Carbamazepine, eslicarbazepine acetate, oxcarbazepine, phenobarbital, phenytoin, rufinamide, topiramate and perampanel are all hepatic enzyme-inducing and will have an impact on contraceptives. These drugs, especially carbamazepine, accelerate OCP metabolism, reducing contraceptive effect. Sodium valproate does not interfere with the oestrogen component of the contraceptive pill, unlike phenytoin and carbamazepine.

Drugs such as levetiracetam, zonisamide, pregabalin, lacosamide, brivaracetam, clobazam and clonazepam are unlikely to effect OCPs.

Lamotrigine needs to be considered as a special case with OCPs. It is a non-enzyme-inducing AED that can lower the amount of progestogen from an OCP but not the oestrogen. There is currently no conclusive evidence that lamotrigine reduces the effectiveness of OCPs, but there is evidence that OCPs lower lamotrigine levels in the blood. This could reduce seizure control and allow seizures to occur.

It is important that any OCP and AED co-prescribing be considered carefully.

- Is the interaction significant?
- Should consideration be given to changing the AED dose or type? Could this lead to risk of losing seizure control?
- Should consideration be given to changing the type of contraception? If so, to what?
- Have the benefits and risks of prescribing contraceptives together with AEDs been discussed comprehensively with the patient or in the best interests of the patient?
- Has advice been taken from a pharmacist?

In women with ID and epilepsy extreme care needs to be taken in prescribing and, more importantly, monitoring OCPs. Evidence-based pathways (Shankar et al, 2013b) should be considered to help support decision-making in prescribing and monitoring.

As discussed, there is a high rate of comorbidity in people with ID and epilepsy. Consequently, they are often co-prescribed psychotropic

medication for mental illness or behavioural disorders which may or may not be directly related to their epilepsy. It is therefore important for prescribers to be aware of the potential interactions that AEDs have with commonly prescribed psychotropic medications (Spina & Perucca, 2002; Johannessen & Johannessen Landmark 2010).

Psychotropic medication

Antidepressants and antipsychotics may inhibit or form substrates for a number of CYP enzymes. As a result, there is potential for interaction with the metabolic and therapeutic effects of AEDs (Spina & Perucca, 2002).

Clozapine, olanzapine, risperidone, haloperidol, thioridazine, ziprasidone, quetiapine, citalopram and reboxetine act as CYP substrates.

Fluvoxamine, fluoxetine, paroxetine and sertraline are CYP inhibitors.

It is good practice to check the medication regime for any significant interactions, particularly when considering adding or withdrawing psychotropic medication. Such medication changes have the potential to affect the efficacy of AEDs and prescribers should consider checking serum drug levels where applicable.

Effects of commonly used psychotropics on seizures

Antipsychotics

A study (Wu et al, 2016) comparing the antipsychotic-related seizure risk of first- and second-generation antipsychotics in patients with schizophrenia and mood disorders reported an overall 1-year incidence rate of 9.6 (95% CI 8.8–10.4) per 1000 person-years. First-generation antipsychotics were marginally associated with a higher seizure risk than second-generation antipsychotics (adjusted hazard ratio: 1.34; 95% CI 0.99–1.81; *P* = 0.061), with certain antipsychotics having higher risk than others. Aripiprazole was found to have lower risk than risperidone (Table 7).

Antidepressants

Most antidepressants are regarded as being safe to prescribe for people with epilepsy (Johannessen Landmark et al, 2016). However, some, particularly older antidepressants, should be avoided or need to be used with caution as they have possible proconvulsant effects (Tables 8 and 9).

The risk of seizures with most antidepressants is low, but it is probably not zero for any of them, and patients should be made aware of this

Table 7 Significant antipsychotics associated with seizure risk compared with risperidone

Antipsychotic	Adjusted hazard ratio (95% CI)*	Level of risk
Clozapine	3.06 (1.40–6.71)	Higher risk
Thioridazine	2.90 (1.65–5.10)	Higher risk
Chlorprothixene	2.60 (1.04–6.49)	Higher risk
Haloperidol	2.34 (1.48–3.71)	Higher risk
Aripiprazole	0.41 (0.17–1.00)	Lower risk

*$P = 0.05$.
Source: Wu et al (2016).

Table 8 Seizure incidence rates and manufacturers' advice for individual tricyclic antidepressants		
Tricyclic antidepressant	Incidence	Manufacturers' advice
Amitriptyline	0.3% (therapeutic doses)	Avoid if possible in patients with a history of epilepsy
Clomipramine	0.5–12.2% (therapeutic doses, dose dependent)	Use with extreme caution in epilepsy (seizure occurrence appears to be dose dependent)
Dosulepin	Limited data	Avoid in patients with history of epilepsy
Doxepin	0.1% (therapeutic doses)	Use with caution in patients with history of epilepsy
Imipramine	0.1% (≤200 mg/day), 1.1% (>200 mg/day)	Use with extreme caution in epilepsy (seizure occurrence appears to be dose dependent)
Lofepramine	Limited data	Use with extreme caution in patients with a history of epilepsy or recent convulsions
Nortriptyline	Limited data	Avoid if possible in patients with a history of epilepsy
Trimipramine	Limited data	Use with great caution in patients with a history of epilepsy
Mianserin	Limited data	Convulsions have been reported at therapeutic dose so use with caution in epilepsy
Trazodone	<0.1% (therapeutic doses)	Use with caution in patients with epilepsy; specifically, avoid abrupt increases or decreases in dose

Source: UK Medicines Information (2016).

Table 9 Antidepressants by class and their seizure propensity		
Antidepressant class	Drug examples	Drugs with propensity to cause seizures and their metabolic pathway
Non-selective monoamine reuptake inhibitors (NSRIs): the TCA group	Amitriptyline, doxepin, nortriptyline, trimipramine	Clomipramine (CYP1A2, 3A4, 2D6)
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine, sertraline	None[a]
Noradrenaline reuptake inhibitors (NRIs) or serotonin–noradrenaline reuptake inhibitors (SNRIs)	Reboxetine, venlafaxine, duloxetine	None
Monoamine oxidase-A inhibitors	Moclobemide	None
Others	Mianserin, mirtazapine	Bupropion (CYP2D6)

a. SSRIs can have a proconvulsant effect in people without epilepsy, but this has not been shown in people with established epilepsy (Curran & de Pauw, 1998; Jackson & Turkington, 2005). Studies are largely in animal models and overdose in humans.

TCA, tricyclic antidepressant.

Source: modified from Johannessen Landmark et al (2016).

when prescribing. The risk of seizures increases with increasing doses. Selective serotonin reuptake inhibitors (SSRIs) are considered the first-line antidepressant option in patients with epilepsy. Fluoxetine is *not* the best choice, because of its long half-life, a possibly greater incidence of seizures and an increased risk of drug interactions. Citalopram or sertraline may be considered better options, because of their safety and reduced interaction potential with AEDs.

As a general rule, the more sedating a drug is, the more likely it is to induce seizures (Taylor et al, 2015). There is a dose-dependent relationship between antidepressant use and seizures. Patients with a history of seizures should be started on a low dose, and this should be increased slowly until a therapeutic dose has been achieved (Taylor et al, 2015; Bazire, 2016). In addition, maximum recommended doses of antidepressants should not be exceeded.

Although it is possible that antidepressant drugs will lower the seizure threshold, this should not get in the way of appropriately treating a depressive disorder in an individual who also has epilepsy. Any changes in seizures should be noted and consideration given to a concomitant increase in AED dose.

Lithium

Lithium is licensed for recurrent depression where treatment with other antidepressants has been unsuccessful (eMC, 2015). Lithium use in epilepsy is cautioned because of its potential to increase the frequency of convulsions at therapeutic doses and it has marked epileptogenic activity in overdose (eMC, 2015; Bazire, 2016). In addition, interactions with carbamazepine may cause neurotoxicity and there are reports of interactions with phenytoin (eMC, 2015).

Commencing, switching, monitoring and withdrawing AEDs

The NICE clinical guideline on epilepsies (CG137) states that clinicians should help individuals with epilepsy and ID and their family or caregivers (if appropriate) to take an active part in developing a personalised care plan that takes any comorbidity into consideration (NICE, 2012: section 1.16). Reasonable adjustments should be made to ensure adequate time for consultation and individuals should have access to all applicable investigations and treatment options. The monitoring of effectiveness and tolerability of treatment should be the same as for the general population, but with particular attention paid to the potential adverse cognitive and behavioural effects of AEDs.

Clinicians should maintain high levels of vigilance for adverse effects of treatment, including bone health and neuropsychiatric problems. It is essential that an individual with epilepsy and ID and their family or carers, if appropriate, are fully informed about the treatment plan and any potential adverse effects. Adjustments should be made to facilitate understanding, including the use of communication aids and advice from other professionals. CG137 states that the maximum time between reviews should be 12 months. It would be good practice to provide a review at least every 3 months, particularly if there are ongoing changes to AEDs. This could be performed remotely, using methods such as telehealth or a telephone consultation.

Commencing and switching medication

NICE and the *British National Formulary* publish high-level evidence on the initiation of AEDs. However, all such advice is from trials and studies done in the general population. What is now becoming accepted is that any new AED prescribed for someone with ID needs to be started at a low dose, with the priority being to establish safety and mitigate side-effects as opposed to achieving quick efficacy. The likelihood of making a difference swiftly in a person with treatment-resistant epilepsy has to be balanced against the risk

of the medication causing side-effects and being withdrawn without having a fair trial. It is essential to start a new AED and build it up to a therapeutic dose before withdrawing an old medication. It is prudent to start low, go slow and to co-prescribe the fewest possible different AEDs. Prescribing more than three is likely to raise the risks of side-effects disproportionately to the benefits provided. If more than three AEDs are in the regime, a clear rationale must be given as to why that is the case and what is being done to reduce the number of AEDs, mitigate their long-term side-effects and justify the positive role of the regime. As already explained, comorbidities and other medications need to be considered when choosing an AED.

Managing medication

In the general population the goals of treatment are clear – seizure freedom, minimal side-effects and improved quality of life – and outcomes are easily assessed. Setting treatment goals and assessing outcomes are more challenging in people with ID, because of the complexity of their condition and the often treatment-resistant nature of their epilepsy. Nevertheless, the ideal is to establish treatment goals before starting treatment, even though they might subsequently prove to be unattainable. Goals should be discussed with the patient and, if appropriate, family or caregivers. The primary goal should be freedom from seizures, but if that is doubtful in practice, acceptable alternatives should be considered. Goals such as seizure reduction, improvements in cognition and improved quality of life may all be appropriate. In assessing outcomes, clinicians must balance the value of any change in seizure profile against any negative effects of AEDs. Over time, a balance between seizure control, cognitive function, behaviour and other factors may need to be agreed.

An objective measure of treatment outcome is essential, in clinical and research settings. Outcome is a continual process and includes not only an assessment of seizure control, but also consideration of side-effects and quality of life. A number of barriers to effective evaluation may be present. Information will, by necessity, be largely inferred from people with limited communication skills and may be subject to ‘diagnostic overshadowing’. A multidisciplinary approach will be required in most cases to obtain reasonable-quality data, as many individuals will have multiple caregivers in a variety of settings, all requiring guidance to produce accurate recordings.

For individuals with epilepsy and ID it is essential that clinicians consider a wider perspective. Epilepsy management is more than monitoring seizures. As clinicians we must take a holistic personalised approach to care. A diagnosis of epilepsy has a broader impact on quality of life, affecting psychological well-being and social functioning. We know that seizure control is not the main determinant of good clinical outcome (Boylan et al, 2004). The Glasgow Epilepsy Outcome

Scale (GEOS) is a useful easy-to-use instrument that may help capture a wide range of clinical and care concerns from individuals and their caregivers. Health practitioners and carers were involved in its development, and it has been shown to have validity and practical utility for clinicians (Espie et al, 2001). The GEOS may be used in conjunction with clinical assessment of seizure control and treatment outcome within the process of measuring change.

Individuals and their families or caregivers will have specific concerns about AEDs, particularly if the proposed medication may have cognitive or behavioural side-effects. Before prescribing, the clinician should clearly describe these potential effects when discussing treatment options. People with ID will often be on multiple therapies and will have tried several AEDs. It is important to place an individual on a treatment pathway that will assess all available treatment options, including those already in place. The first step is to appraise the current AED therapy. If there is inadequate epilepsy control, but evidence of efficacy and scope to increase the dose of AED, then do so while monitoring closely for adverse side-effects. If this is not successful, then remove the AED to avoid unnecessary polypharmacy. If the individual is prescribed multiple AEDs then remove any drugs that have demonstrated a lack of efficacy. If seizure control is still inadequate, the clinician should consider whether all 'new' AEDs have been trialled and also whether a surgical procedure is merited.

Many people with ID have family members or caregivers who can help in giving treatment. The clinician will need to ensure that carers are capable of providing this support. The NICE guideline CG137 (NICE, 2012) notes that these individuals may require formal training for this role. Seizure recording is important. However, specific help will be needed to count each type of seizure accurately, although it may be very hard to assess alteration in absences.

Many people with ID and epilepsy are on repeat prescriptions of various medications from primary care to treat the significant comorbidity that is often present. It is important to ensure that drug regimes are closely monitored, and NHS England (2015, 2016) pledged to take action to address over-prescribing of psychotropic drugs to these individuals. The community or GP practice pharmacist can play a crucial role in ensuring that this happens, and medicines use reviews (MURs) can help this process (http://psnc.org.uk/services-commissioning/advanced-services/murs).

As people taking multiple AEDs or those taking one AED for more than 5 years are at increased risk of bone loss (Pack & Morrell, 2004), and lower bone density is more prevalent among people with ID than in the general population, the primary care pharmacist can also help in promoting lifestyle measures to improve bone health and reduce the risk of osteopenia, osteoporosis and fractures associated with seizures (Centre for Pharmacy Postgraduate Education, 2017: pp. 40–41).

Drug monitoring

NICE guideline CG137 (NICE, 2012) states that routine drug monitoring is not recommended and should only be performed if there is an identified indication. For example, some AEDs (such as phenytoin) have a narrow therapeutic window secondary to zero-order kinetics and therefore there is a safety concern when adjusting the dose: if toxicity is suspected with such drugs, then blood serum levels should be checked. Serum levels should also be checked should there be any concern about toxicity with other AEDs. Other indications for monitoring may be to confirm adherence and concern over pharmaco-kinetic interactions.

Percutaneous endoscopic gastrostomy (PEG)

Long-term feeding by PEG is uncommon but can present significant problems when both nutrition and medication have to be fed down the same tube. This is especially important in people with epilepsy, for whom the dose and bioavailability of AEDs is critical to maintaining adequate seizure control (Jory et al, 2017). In such cases, measuring the serum concentration of AEDs that have increased pharmacokinetic variability can have a valuable role (Patsalos et al, 2008). The *Handbook of Drug Administration via Enteral Feeding Tubes* (White & Bradman, 2011) offers national guidance, and clinicians have a responsibility to ensure bioequivalence between formulations to avoid treatment failure or toxicity. If they do not have bioequivalence data to hand, we recommend that they liaise with a pharmacist or possibly with the drug company to obtain up-to-date details.

Withdrawing medication

NICE guideline CG137 (NICE, 2012) tells us that any decision to withdraw AEDs should be taken following detailed discussion with the individual, their family/carers and their epilepsy specialist. The specialist must manage the withdrawal. The risks and benefits of continuation or withdrawal must be explored in full for those who have been seizure free for at least 2 years (in some cases for up to 5 years).

A number of cohort studies have examined the reduction of AEDs in the ID population. A study by the MRC Antiepileptic Drug Withdrawal Group (1991) demonstrated that ID is not necessarily a barrier to AED withdrawal: therapy was successfully withdrawn for 40% of seizure-free individuals.

Owing to the comparatively high incidence of refractory epilepsy in people with ID, many individuals will require lifelong treatment.

The decision to begin the slow withdrawal of medication must be based on an evaluation of the potential benefits of being on AEDs *v.* the risk of seizure recurrence on withdrawal. It may be difficult to quantify the potential benefits of medication withdrawal, and assessments of individuals and their particular circumstances are required. Similarly, the potential impact of seizure recurrence may vary widely between individuals and necessitates debate. It is estimated that withdrawing treatment probably doubles the risk of further seizures, with the greatest risk of recurrence in the 2 years immediately after withdrawal. The risk of further seizures varies widely, but a number of risk factors are thought to be associated with poorer outcomes. Individuals with severe ID and gross neurological deficits have a high probability of seizure recurrence. Those receiving AED polytherapy have a tendency to do worse on treatment withdrawal than those whose seizures have been controlled by a single drug (Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1991).

The withdrawal process should be underpinned by awareness of potential risks, including sudden unexpected death in epilepsy (assessed using structured evidence-based tools such as the SUDEP and Seizure Safety Checklist (https://sudep.org/checklist)), and the need for surveillance, especially at night.

Capacity and consent

If there is concern that the individual lacks capacity to make treatment decisions, a capacity assessment under the Mental Capacity Act 2005 must be completed. If the individual is deemed unable to give informed consent, then a best interests decision involving all key stakeholders, including if appropriate an independent mental capacity advocate, should be made. The views of the individual, their family and carers, and the multi-disciplinary team, must be carefully recorded.

Conclusion

AEDs are the mainstay of treatment for epilepsy in individuals with ID. Appropriate skilled use should reduce the health inequalities experienced by this population. Professionals treating this population should recognise and acquire the appropriate knowledge and competencies necessary to deliver such skilled treatment. The WHO in its 2012 review concluded that 'There is a paucity of good quality data on the choice of pharmacological and psychosocial interventions in this special population group, thus more research (intervention data, behavioural and cognitive safety) is needed in this population' (World Health Organization, 2012: pp. 7–8).

There is limited specific evidence to guide clinicians in the prescription of AEDs for people with epilepsy and ID. This document summarises the current evidence and provides informed opinion on prescribing that may be used to help guide prescribing practice. This is done with an acute awareness of the current gaps in our knowledge and in the evidence base.

The primary concern of the clinician considering prescribing AEDs for someone with ID must be the principle '*primum non nocere*' – first, do no harm. The risks and benefits of treatment and of no treatment should be discussed before prescribing, along with any potential adverse effects of medication. It is particularly important to establish whether the individual has the capacity to make informed decisions about their medical care: if they do not, the proposed treatment must be discussed with stakeholders in a best interests meeting. There is a rising awareness of the health and social needs of this vulnerable population, leading to an optimistic view that person-centred treatment evidence might be just round the corner.

Case vignettes

To treat or not to treat?

Vignette 1

James, who is 47 years of age, has severe ID, autism and well-controlled epilepsy. Following his father's death a year ago there was a relapse in seizures, which was put down to bereavement and changes in stress. However, after 6 months the seizures had not reduced despite increase in AEDs to which he had responded well in the past. A review by health and social care professionals that included a carer assessment revealed that James's mother was struggling to cope with his needs, resulting in impairment in his daily quality of life and a lack of the day-to-day structure which used to stabilise his anxiety. A reassessment and review of his needs, with clear structuring of his daily activities, led to freedom from seizures again within 6 months without any further medication changes.

Vignette 2

Pauline is a 28-year-old with severe ID, autism and epilepsy who has attended the emergency department several times in the past 3 months because of seizures. A holistic review showed that a person with terminal dementia had been moved to the room next to hers in the residential home. At night, the disturbances caused by this resident and the staff caring for her were interrupting Pauline's sleep, making her more vulnerable to seizures. A move to a room in a quieter section of the home reduced her seizures by 75% and completely stopped emergency department attendances.

Understanding syndromes

Vignette 3

Mary has Rett syndrome and severe to profound ID. She presented with brief apnoea attacks with no associated symptomology to aid diagnosis of whether these attacks were of seizure origin. She would not cooperate to have an ambulatory EEG. As there is seizure association of >90% in Rett syndrome, a trial of AED was attempted. Mary's apnoea attacks receded with each dose increase until they ceased completely.

AEDs and behavioural pitfalls

Vignette 4

Mark is 20 and has mild ID, transient mood disorder and Down syndrome. At his local hospital he was diagnosed with epilepsy and started on levetiracetam without full consideration of his psychological problems. With each increase in dose as advised by the BNF, the levetiracetam improved his seizures but worsened his mood and behaviour. He became aggressive and violent and was started on risperidone by his GP. This improved his behaviour, but caused a worsening of his seizures. Eventually, when referred to a specialist in ID and epilepsy, sodium valproate was commenced and titrated and, on stabilisation, the risperidone and levetiracetam were gradually withdrawn one by one.

Vignette 5

Katie is a 48-year-old with severe ID and treatment-resistant epilepsy. When transferred to a service specialising in management of ID and epilepsy she was on 6 AEDs. Over a 3-year period her medication regime was rationalised to 2 AEDs. Levetiracetam was used as the 'stock' AED and gradually increased. Four weeks after one such increase, services were contacted for an emergency review and possible reduction of levetiracetam because Katie's behaviour had become challenging and she was refusing to undertake her personal hygiene routines. At the onsite enquiry it transpired that Katie's challenging behaviour was specific to getting into the shower and was not generalised to other activities during the rest of the day. The team occupational therapist tested the shower and found that the hot water valve had failed. A subsequent investigation showed that the shower had been dysfunctional for over 6 months, but the highly sedative effect of the drugs that Katie had been on, and possible ongoing seizure activity, had reduced her awareness so she had not reacted. On rationalisation of her medication and improvement in her personal awareness she was acutely aware that the water was too hot and, lacking communication skills and being non-verbal, she remonstrated by exhibiting 'challenging' behaviour. Had the faulty valve not been noticed, this could have been wrongly attributed to the medication changes that had helped her become better.

Complex case management

Vignette 6

Adam is 26 years old with a rare genetic syndrome leading to severe ID and epilepsy. The epilepsy has been in remission for over 4 years and he is on liquid levetiracetam. Owing to significant weight loss and its implications for Adam's health, a percutaneous endoscopic gastrostomy (PEG) operation was done. He was recently referred with

concerns about relapse of seizures, even though the same medication was being delivered through the PEG. Initially, the seizures were thought to be an outcome of his physical health problems and the stress of surgery. However, when they did not abate a detailed enquiry was undertaken, including a best interests meeting that involved the pharmacist. The pharmacist found that the liquid levetiracetam formulation contained maltitol as a stabiliser, and this substance can speed up gut transit time. Thus, suboptimal efficacy might have been related to inadequate absorption in the gut. When switched to levetiracetam granules, which did not contain maltitol, there was swift improvement. In a short period Adam went back to seizure remission.

Medication side-effects

Vignette 7

Susan, aged 46, has moderate ID with seizures that have been in remission for over 5 years; she is on sodium valproate 2000 mg/day and haloperidol. She presented with a 5-month history of lassitude, tiredness, falls and minor confusion, and having had three episodes of respiratory infection requiring antibiotic treatment. There was a recurrence of seizures with the infection and the GP believed this to be secondary to the high temperature occurring with the infection. Initially, it was thought that she might be going through the menopause. A full blood count among other blood tests revealed thrombocytopaenia. The sodium valproate was gradually reduced to 1500 mg/day and a re-test of full blood count after 3 months showed full recovery. Along with this, her problems of tiredness, infections, seizures and falls stopped.

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