Intellectual Disability and Epilepsy

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Abstract	Epilepsy in people with intellectual disability is more than the sum of the two conditions. Diagnosis is challenging in the face of cognitive and communication difficulties and in some instances the need to rely on third party information and difficulties in accessing relevant investigations. Treatment is complicated by the lack of evidence specific to intellectual disability and associated neurodevelopmental comorbidities. The presence in many with associated physical and psychological co-morbidity in the face of treatment resistance and increased preponderance to side effects and challenging behavior makes epilepsy management in people with intellectual disability highly complex. It can be argued that specific understanding and skill sets are needed to help manage this vulnerable group. This book chapter looks to outline the unique challenges and questions to treatment this special population poses and looks to provide evidence based up to date answers where available.
Keywords (separated by " - ")	Epilepsy - Seizures - Intellectual disability - Learning disabilities - Mental retardation - Pervasive developmental disorder - Autism - Epileptic encephalopathies - Premature mortality - SUDEP - Challenging behavior - Neuropsychiatric - Treatment choices - Antiepileptic medication side effects

Q1

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Intellectual Disability and Epilepsy

10

Rohit Shankar, Lance Watkins, and Stephen Brown

10.1 Introduction

Epilepsy is a chronic disorder of the brain characterized by a predisposition to seizure activity, and associated with long term neurobiological, psychological, and social effects. A seizure can be defined as a transient occurrence of neurological symptoms associated with abnormal neuronal activity in the brain. The semiology of the seizure event will vary dependent upon the origin of the abnormal or excessive neuronal activity and may present with sensory, motor, emotional, or behavioral disturbance [1]. Two unproved seizures with at least a day apart were needed to diagnose epilepsy but The International League against Epilepsy (ILAE) Task Force has since refined this definition. Now clinicians are advised to consider an epilepsy diagnosis in individuals with *one* unprovoked seizure in association with other known risk factors [2].

AU2

10.2 Classification

The new Classification of the Epilepsies developed by the ILAE Commission for Classification and Terminology proposes a multilevel classification system. Clinician's should aim to make a diagnosis at all levels (dependent upon

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t1.1 **Table 10.1** ILAE (2017) classification of seizure types [4] AU3

t1.2 Focal Onset	Generalized onset	Unknown onset
t1.3 t1.4 **Aware/Impaired awareness**		
t1.5 **Motor**	**Motor**	**Motor**
t1.6 t1.7 t1.8	Tonic-clonic Other motor (myoclonic, tonic, atonic, mixture)	Tonic-clonic Other motor (myoclonic, tonic, atonic, mixture)
t1.9 **Non-motor**	**Non-motor** (absence)	**Unclassified**
t1.10 t1.11 Focal to bilateral tonic-clonic		

resources), while considering etiology of the epilepsy throughout the assessment process [3] (Table 10.1).

1. *Seizure Type*—seizures are classified focal, generalized, and unknown onset.
2. *Epilepsy type*—as well as the seizure types above, good practice now considers combined generalized and focal epilepsy. Such diagnoses are likely to require investigations including characteristic findings on electroencephalogram (EEG).
3. *Epilepsy syndrome*—Cluster of symptoms including clinical history, seizure type, EEG changes, typical findings on neuroimaging (MRI), and genetic testing.

10.3 Epidemiology

The estimated prevalence of epilepsy in the general population may be anywhere between 0.6 and 1% [5]. In comparison, the prevalence of epilepsy in the intellectually disabled population ranges between 14 and 44% depending upon case ascertainment, with a proportional relationship with level of intellectual disability (Table 10.2) [6–11]. An overall prevalence of 22% has been shown based on a pooled meta-analysis of the data currently available [12].

Despite the clear relationship between epilepsy and intellectual disability understanding this association can be complex (Table 10.3). There may be a wide range of pathological processes influencing neurodevelopment at varying stages [25, 26]. This suggests multifactorial etiology which often results in multiple co-morbid conditions. People with intellectual disability and epilepsy have more physical co-morbidities than those with intellectual disability without epilepsy, which results in higher health costs and increased mortality rates [27]. Intellectual disability in combination with epilepsy significantly raises standardized mortality ratios and the highest rates of mortality are associated with a high frequency of generalized seizures and profound intellectual disability [28]. In a UK investigation seizures and epilepsy were the most frequent cause of potentially avoidable hospital admissions in people with intellectual disability, equating to 40% of all emergency admissions in adults with

Table 10.2 Prevalence of epilepsy and level of intellectual disability [12]

Mild	10%
Moderate, severe, profound	30%

Table 10.3 Epilepsy syndromes and epilepsy phenotypes associated with intellectual disability

Syndrome	Genetic abnormality	Epilepsy phenotype	Management
Dravet syndrome (severe myoclonic epilepsy)	SCN1A mutation	Febrile and non-febrile seizures in first 12 months of life Episodes of status epilepticus Intellectual decline in second year	Sodium channel blockers-Lamotrigine, phenytoin, and carbamazepine can aggravate seizures [13]
Tuberous sclerosis	TSC1, TSC2	69% epilepsy [14] Onset in infancy, 30% infantile spasms. Infantile spasms-typical hypsarrhythmia EEG pattern [15]	May respond well to Vigabatrin [16] Noval therapeutic options include mTOR inhibitors [17]
GLUT1 deficiency	SLC2A1	Seizures in first 4 months of life Dystonia-including exercise induced dyskinesia	Ketogenic diet [18]
Down's syndrome	T21	Two peaks in seizure onset-first year of life after the age of 40 [19] Seizures may be associated with Alzheimer's dementia-generalized myoclonic seizures of high frequency and severity	Caution with AEDs with adverse cognitive profiles if dementia diagnosis present
Lennox-Gastaut syndrome (epileptic encephalopathy)		*Classic triad-* Seizures-multiple types, treatment resistant EEG findings-diffuse slow spike wave activity (≤2.5 Hz), with fast activity during sleep ID and neuropsychiatric symptoms [20]	Rufinamide may offer most benefit [21] Lamotrigine-improved seizure control, mood, and sociability [22] Clobazam-useful adjunct [23] Topiramate-improvement in drop attacks [24]

intellectual disability [29]. Both epilepsy and intellectual disability are individually associated with psychiatric co-morbidities. In people with intellectual disability and active epilepsy there is further increased risk of mental illness [30]. The assessment of behavior and neuropsychiatric side effects in people with epilepsy and intellectual disability can be complex and require a multidisciplinary approach.

People with intellectual disability and epilepsy are more likely to experience treatment resistant seizures with up to two-thirds showing a poor response to

t4.1 **Table 10.4** Important aspects of Epilepsy history

t4.2 *Description of event*—Pre-ictal, Ictal, Post-ictal (abnormal movements, abnormal tone, warning signs (aura), triggers, duration, day/nocturnal, frequency, any other events, injuries/complications—e.g., head injury, difficulty breathing.
t4.5 *Inter-ictal changes*—mood, personality, behavior.
t4.6 *Past history*—previous seizures/progression of epilepsy, history of febrile seizures as a child, previous history of head injury, history of significant medical conditions, genetics, family history of epilepsy or neurological disorder.

anti-epileptic medication [8]. The combination of intellectual disability, treatment resistant epilepsy, and neurological deficits is often associated with genetic abnormalities or underlying structural pathology [31]. Uncontrolled epilepsy can have serious negative consequences on both quality of life and mortality [32]. There is a limited evidence base to support the prescribing of anti-epileptic medication in this vulnerable population [33] Supporting people with intellectual disability and epilepsy especially those with poorly controlled epilepsy requires high levels of competence and confidence in staff in community settings [34].

10.4 Diagnosis

Epilepsy is primarily a clinical diagnosis and should be made by a medical practitioner with training and expertise in epilepsy. In order to establish a diagnosis of epilepsy a thorough history is required with good collateral information and witness reports of the event (Table 10.4). This is particularly important for people with intellectual disability who may have cognitive and communication deficits. It is preferable to obtain a detailed description of events including the pre-ictal, ictal, and post-ictal period. It is useful if this information is provided in a standardized way using validated seizure monitoring tools [35]. There may be benefit in video-recording events. This will require the consent of the patient, or if the individual lacks capacity a formal review should take place with all interested parties to assess whether it is in the individuals best interests.

10.5 Differential Diagnosis

There are a wide range of events that can mimic the presentation of a seizure (Table 10.5). Identifying a seizure disorder in the intellectual disabled population is further complicated by levels of cognitive impairment, communication difficulties, and associate co-morbidities. People with epilepsy and intellectual disability have higher rates of stereotyped motor behaviors often associated with neurodevelopmental disorders such as autism [36]. It has been shown that up to 25% persons with intellectual disability and epilepsy referred to a specialist center have been misdiagnosed [37].

Table 10.5 Differential diagnoses for seizures in people with intellectual disability t5.1

Cardiac—Syncope (vasovagal, orthostatic hypotension, arrhythmia)	t5.2
Psychological—panic attack, dissociative disorder, psychosis, affective disorder, Non epileptic seizure	t5.3 t5.4
Behavioral disorder—stereotypies, sensory seeking behavior- including self-injurious behavior (SIB), compulsions	t5.5 t5.6
Vascular—migraine, transient ischemic attacks (TIA), transient global amnesia (TGA)	t5.7
Metabolic—hypoglycemia, insulinoma, hypernatremia, hypocalcaemia	t5.8
Sleep disorder—parasomnia, narcolepsy, enuresis, nightmares	t5.9
Movement disorder—paroxysmal dyskinesia	t5.10
Toxic state—alcohol, illicit substances, toxicity of prescribed medication	t5.11

10.6 Epilepsy and Behavior 86

There are some key differences to be mindful of when considering the difference between a seizure and a behavioral disturbance. As a rule a seizure usually presents with similar behavior during each event. There is generally no clear precipitant and the individual will be unresponsive to attempts to communicate during the event. There is also the potential for behavioral or neuropsychiatric disturbance to occur as part of the complex epilepsy course. These symptoms may present during the peri-ictal (pre-ictal, ictal, post-ictal) or inter-ictal period. There are added complexities to consider in the pharmacological management of epilepsy including the potential neuropsychiatric effects of AEDs, and the impact of psychotropic medications on seizure control. 87 88 89 90 91 92 93 94 95 96

10.7 Investigations 97

A special report by the UK chapter intellectual disability working group of the ILAE has shown that people with epilepsy and intellectual disability wait longer for routine investigations including EEG and MRI brain imaging [35]. This may be a result of inequality in access to specialist care provision [34]. Services need to ensure that the reasonable adjustments required are put in place so that this vulnerable population have access to the relevant investigations required [35]. The use of video EEG alongside telemetry can be particularly helpful in differentiating seizures from other behaviors in this population. It has been shown that there is a high rate of abnormality detection on MRI brain in those individuals with intellectual disability who undergo investigation [38]. 98 99 100 101 102 103 104 105 106 107

It is important to note that a normal EEG between seizures does not rule out epilepsy. The ideal scenario is to capture an event during the EEG recording. The presence of epileptiform activity on EEG is also possible in people without epilepsy, particularly people with intellectual disability [39]. MRI has essentially replaced CT as the imaging of choice for epilepsy because of its sensitivity and specificity in identifying structural lesions that could be the origin of epileptic 108 109 110 111 112 113

discharges. However, MRI is not always widely available, and CT may be the most appropriate choice in an emergency. It is not uncommon for people with intellectual disability and associated co-morbidities to find it difficult to tolerate brain imaging. It may necessary to use sedation or even general anesthetic in order to complete investigations that require such an investigation in the person's best interest. If this is the case then capacity of the individual to consent must be assessed. Where the individual lacks the capacity to make an informed decision there should be a formal best interest's process as identified by the local legal processes weighing up the benefits and risks of such procedures and recorded accordingly. Electrocardiogram (ECG) and laboratory blood investigation are also an important part of the diagnosis process and will help rule out any potential other causes of events.

10.8 Treatment

A mainstay of epilepsy treatment is the prescription of AEDs. To date there is very little evidence-based research for AED prescribing in people with ID [33]. A Cochrane review into the pharmacological interventions for epilepsy in people with ID highlights the lack of evidence to support the efficacy, side-effect profile, and safety of AEDs for people with ID [40]. The treatment of epilepsy requires a person-centered approach with consideration to each stage of the ILAE classification of epilepsies [4]. This is perhaps more relevant to the ID population where there will be particular concerns over the potential cognitive and behavioral side effects of AEDs.

10.8.1 Pharmacological Management

A large proportion of people with intellectual disability and epilepsy experience a chronic refractory course, with up to 40% receiving multiple AEDs but still experiencing poor seizure control [41]. In the UK the Royal College of Psychiatrists (RCPsych) College Report CR206 (2017) is a technical paper advising on the prescription of AEDs for people with epilepsy and intellectual disability, based on current evidence. This paper explores the potential for drug interactions, AED formulation, and the management of neuropsychiatric co-morbidities. The College Report provides a simplified 'traffic light system' (first line, second line, and avoid) approach to AED prescription for people with intellectual disability.

The adverse effects of AEDs are more commonly observed when high doses are prescribed and dose titration is rapid [42]. Therefore it is recommended that AEDs are introduced at low dose and titration is slow, reducing the likelihood of dose related adverse effects. When adding a new drug it is recommended that a therapeutic dose is established before removing the old drug. This will help attribute any changes in efficacy or side effect profile more easily [43].

10.9 Lamotrigine (First Line)

Lamotrigine has been shown to be well tolerated in the intellectual disability population, with good efficacy in seizure control and improvement on a range of quality of life measures [44]. Lamotrigine is known to have mood stabilizing properties and a randomized open-label investigation not only showed improved seizure control but improvements in challenging behavior [45]. There is specific evidence to show that Lamotrigine improves seizure control and a wide range of quality of life and social measures in people with Lennox-Gastaut syndrome [46].

10.10 Sodium Valproate (First Line)

The evidence suggests that valproate is a broad spectrum treatment option that can be used for a variety of seizure types with a good safety profile [47]. It is a first-line treatment for primary generalized seizures and is recommended for use for people with treatment resistant seizures, and people with intellectual disability may be more responsive [33]. The main limitations to the widespread use of valproate are the side effect profile. Along with more common effect such as weight gain, valproate is known to have significant teratogenic effects and is therefore not recommended for women of child bearing age. This needs careful considerations in the intellectual disabled population for any women with borderline or mild intellectual disability who may be sexually active.

10.11 Topiramate (Second Line)

The efficacy of topiramate has been investigated through a number of randomized, placebo-controlled, add-on design trials. These investigations show good improvements in seizure control, however the power of the studies is too low to demonstrate statistically significant findings. Importantly no significant effect on behavior was observed [48]. There is evidence that topiramate may be effective against a wide range of seizure types, particularly dangerous atonic seizures observed in Lennox-Gastaut syndrome [49].

10.12 Levetiracetam (Second Line)

Levetiracetam appears to be generally well tolerated in the intellectual disabled population with improvement in seizure control and increased seizure freedom rates in open study designs [50]. An association between levetiracetam and neuropsychiatric side effects, particularly aggression has been observed, and these effects may be more common in people with intellectual disability [51]. As with most AEDs, the risk of neuropsychiatric side effects increases with a previous psychiatric history [52].

10.13 Carbamazepine (Second Line)

There is a very limited evidence base to support the efficacy of carbamazepine specifically in people with intellectual disability. There is evidence to suggest that slow release preparations may be better tolerated in the intellectual disabled population [53]. Carbamazepine in known to have a number of associated adverse effects including hyponatremia, sedation, dizziness, and bone marrow suppression. Carbamazepine also interacts with many other drugs which can significantly alter their efficacy and requires consideration before prescribing [43]. *Oxcarbazazepine* has been investigated in on add on trial in children with good efficacy but relatively poor tolerability with the need for dose reduction or discontinuation in one fifth of cases [54].

10.14 Lacosamide (Second Line)

An open label retrospective investigation suggests that lacosamide may be a useful adjunct for people with intellectual disability and treatment resistant epilepsy. However, the evidence base is very limited and caution is therefore advised with interpretation [55].

10.15 Perampanel (Second Line)

In a multi-center retrospective case series perampanel was found to be safe and well tolerated, with good improvement in seizure control as an adjunctive agent [56]. However, there is evidence to suggest an increased risk of psychiatric side effects in people with intellectual disability. A cross sectional study identified that over half of the patients involved experience behavioral changes, most notably aggression [57]. It is therefore advise that caution is taken if prescribing for individuals with a previous history of behavioral disorder or psychiatric illness.

10.16 AEDs to Avoid

Older AEDs such as phenobarbitone and phenytoin should not be prescribed for people with intellectual disability without good reason and only if it is in that individuals best interests. Such medications are associated with significant side effect profiles including a detrimental impact upon cognition, behavioral disturbance, multiple drug interactions, and encephalopathy at toxic levels [58].

10.17 Other AEDs

Newer AEDs have little to no evidence base for prescribing for people with epilepsy and intellectual disability. AEDs such as pregabalin, brivaracetam, tiagabine, and zonisamide may be used more routinely in clinical practice as second/third/fourth

line agents for treatment resistant seizures. However, efficacy, safety and tolerability have yet to be rigorously assessed in this population.

The UK Ep intellectual disabilities—research Register is a National Institute of Health Research adopted project undertaking a retrospective cohort study of real world outcomes, including tolerability and efficacy of AEDs in people with epilepsy and intellectual disability [33]. A recent investigation into perampanel by the Register has highlighted that people with moderate to profound intellectual disability are less likely to drop out- possibly due to their inability to report or communicate subjective side effects. This lower dropout rate was associated with higher rates of seizure improvement due to higher rates of retention and compliance [56]. Health care professionals have a role in educating patients, caregivers and families to understand epilepsy, the rationale for treatment, reduce stigma, and developing positive relationships. People with intellectual disability and their caregivers may not understand the importance of adhering to a treatment regime. A simple regime, the use of pictures and close liaison with the pharmacist all help. The use of pictures to communicate with people with intellectual disability can help such as the Books beyond words series [59].

10.18 Non-Pharmacological Interventions

10.18.1 Epilepsy Surgery

Intellectual disability is not, and should not be considered a contraindication for resective surgery [60]. In fact there is evidence to demonstrate that surgical intervention can improve both the behavioral and cognitive functioning of some people with epilepsy and ID [61]. For people with intellectual disability and treatment resistant epilepsy surgical intervention has been associated with improvement in seizure freedom compared to medical treatment, alongside improved quality of life measures [62].

10.18.2 Vagus Nerve Stimulation

Vagus nerve stimulation is indicated for use as an adjunctive therapy and can reduce the frequency of seizures in adults who remain refractory with AED treatment, and are not suitable for resective surgery [63]. Vagus nerve stimulation is a relatively safe surgical intervention for patients with intellectual disability [64]. There are some important short and long-term effects of vagus nerve stimulation to consider including the potential for impact upon normal cardiac conduction [65].

10.18.3 Ketogenic Diet

A Ketogenic diet is essentially high in fat and low in carbohydrates. There is evidence to support its efficacy in improving seizure control, specifically in Dravet

syndrome and Glut1 deficiency [66]. However, a Cochrane review of non-pharmacological interventions for adults with epilepsy and intellectual disability shows the lack of evidence available in this population. One of the main drawbacks of the diet is its tolerability [67].

10.19 Risk Management

The risks associated with epilepsy can be complex and wide ranging. We have to consider the impact of seizures themselves upon mortality, injury, and hospitalization. We also have to appreciate the wider impact of a chronic epilepsy course upon psychological, emotional, and social functioning. The approach to risk assessment and management should be person centered and evidence based. This will usually involve assessing the patient's level of risk and depends on the individual, their environment, frequency and severity of epilepsy. There are certain risks that are increased with people with intellectual disability and it is important that healthcare professionals are aware of these higher risks and discuss them with the individual, their families and/or caregivers. Any assessment should also include a basic analysis of risk associated with bathing and showering, preparing food, using electrical equipment, managing prolonged or serial seizures, the impact of epilepsy in social settings, and the suitability of independent living [68, 69].

10.20 Sudden Unexpected Death in Epilepsy (SUDEP)

Sudden unexpected Death in Epilepsy is the sudden and unexpected death of a person with epilepsy when no identifiable cause of death is made following post-mortem examination and toxicology [70]. The diagnosis of SUDEP is not straightforward and is essentially one of exclusion. The classification of SUDEP has more recently been further refined [71]. The incidence of sudden death appears to be 20 times higher in patients with epilepsy compared to the general population, and SUDEP is the most common cause of epilepsy related death [72]. The risk of SUDEP is increased for people with intellectual disability and treatment resistant epilepsy [73]. The UK NICE Clinical guidelines on the epilepsies [60] recommend that patient's, caregivers and families need to be counselled using information tailored to the patient's relative risk of SUDEP. The SUDEP and Seizure Safety Checklist is an evidence based tool that can be used to both assess and communicate risk with patient, their families and caregivers [72]. Effectively assessing and managing risk factors using a person centered approach can reduce the number of epilepsy relate deaths in people with intellectual disability (Table 10.6) [74–76].

Table 10.6 Desirable standards of care in the management of SUDEP [77] t6.1

• Seizure frequency: maximize seizure control (GTC and nocturnal seizures) with pharmacological and non-pharmacological treatment. Aim for less than 3 seizures pre year.	t6.2 t6.3
• Collateral risk: Work collaboratively with patient, families, and caregivers to deliver person centered risk reduction. Including advocating nocturnal supervision where indicated.	t6.4 t6.5
• Access to care: Ensure equitable access to specialist review and reasonable adjustments for people with intellectual disability.	t6.6 t6.7
• Comorbidities: Detailed assessment of physical and psychological co-morbidities including genetic testing, and liaison with relevant specialists.	t6.8 t6.9

10.21 Status Epilepticus 291

People with intellectual disability are more likely to experience status epilepticus and associated mortality rates are higher [78]. Status epilepticus is an emergency and may warrant the prescription of a rescue medication protocol to reduce the risk of potential harmful effects. Treatment should be given if the individual has a prolonged convulsive seizure that lasts for 5 min or more or if seizure occurs 3 or more times in an hour [60]. Rescue protocols can and should be adapted to ensure they are tailored specifically to an individual's needs and identified risks. Standardized guidelines on training standards and practice are available from the Joint Epilepsy Council of the United Kingdom and Ireland. Any rescue medication must be administered by an appropriately trained person. Training should include an overview of epilepsy and associated risk factors in order to help ensure safe administration of rescue medication by family members or care staff. Treatment options available in the community include buccal midazolam (first-line treatment) and rectal diazepam (if midazolam is not suitable).

Benzodiazepines can be used as both rescue medication and as an effective add-on treatment in refractory epilepsy. Clobazam in particular is recognized as being especially useful as intermittent rescue treatment, often used to manage cluster seizures. Clobazam is considered appropriate to use regularly as second line or adjunct therapy for all major seizure types. A major concern is the development of tolerance, however around 30% of people with epilepsy prescribed clobazam could continue without experiencing long-term tolerance [33].

Conclusion

The management of epilepsy in the intellectual disabled population is complex, not least owing to the level of cognitive impairment and communication difficulties. The intellectual disabled population is more likely to have treatment resistant epilepsy and multiple associated co-morbidities. Each case requires a person centered approach considering all aspects of epilepsy including seizures themselves, risk assessment, and the psychological and social impact of a multifacto-

rial chronic disorder. The UK RCPsych has published two recent college reports detailing delivery of epilepsy care [79] and the approach to prescribing [43] for people with intellectual disability.

The delivery of epilepsy care to people with intellectual disability has been shown to be fragmented and at times inadequate due to inequalities in access to specialist care [34]. There is a need for improved collaboration between all professional bodies involved in the delivery of care to this population, with improvement in standards of assessment, information gathering, and the education and training of healthcare staff, families or caregivers [35].

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Author Queries

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Queries	Details Required	Author's Response
AU2	Please check the hierarchy of the section headings and confirm if correct.	
AU3	Please check whether the presentation and placement of Tables 10.1 to 10.6 are okay as typeset.	
AU4	As per style references have been changed from "name and year" to "numbered" format. Please check whether the citations are appropriate.	