Prescribing for epilepsy in adults with Intellectual Disability: A serious conundrum

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Abstract

Background:

About a quarter of people with epilepsy have Intellectual Disability (ID). This group has communication issues, premature mortality, more treatment resistance, difficulties in making informed choices and greater risks of physical and mental health co-morbidities. There is no specific prescribing guidance for this large and vulnerable group. We reviewed the literature on prescribing for epilepsy in this group, in particular examining how anti-epileptic drugs (AEDs) work regarding their side effect profiles, effects on specific epilepsy syndromes associated with ID and their individual strengths and weakness based on the nature and degree of ID.

Method:

A narrative review for which a comprehensive search was conducted to identify evidence for prescribing commonly used AEDs to people with ID including genetic syndromes specifically associated with epilepsy.

Results:

A detailed analysis of the results has highlighted the urgent requirement for suitable and reliable evidence in AED prescribing amongst adults with epilepsy and ID as no studies taking account of the response to AEDs of the ID populations based on the WHO/DSM criteria of clinical severity of ID were identified.

Conclusion:

There is a significant shortfall in suitably powered studies to provide sufficient evidence for safe prescribing of AEDs to people with ID.

Background:

Approximately 600,000 people in the UK have a diagnosis of epilepsy and many take antiepileptic drugs (AEDs). Worldwide, the prevalence of epilepsy is likely to be between 0.5 to 1% [1]. Around one quarter of people with epilepsy (PWE) have an ID (defined as a Full Scale Intellectual Quotient (IQ) <70) [2]. Half of the people with IQ < 50-55 have epilepsy and up to 50% have treatment resistant epilepsy with a heightened risk of harm due to seizures. This population has significantly higher representation of mental health and physical health co-morbidities and usually have complex health needs [3]. Cognitive impairment and communication difficulties leave individuals at risk of making poor health choices and enhance the risk of poor choices being made for them [3]. For people with ID, convulsions remain the main cause for avoidable hospital admissions and currently account for 40% of all emergency hospital admissions [2].

The presence of ID has a number of potential influences on the prognosis of an individual's epilepsy and similarly epilepsy can have a worsening effect cognitively and socially on people with ID. There is currently no available comprehensive system in the UK which requires the details of an individual's ID to be registered at the time of death. Estimates from death certificates suggest around 1000 deaths occur each year in individuals with an ID but this figure is open to bias and misinterpretation [4]. The National Learning Disability Review Development Project identified that life expectancy for individuals with ID is 16-24 years less than the general population with rates increasing with the severity of ID and existence of co-morbidities including epilepsy. There are two main causes of preventable death in people with an ID and epilepsy: aspiration pneumonia and epilepsy or convulsions [4]. Further guidelines and investigation are warranted related to the potential influence ID has upon the prognosis of epilepsy and management and vice versa to ensure all receive effective treatment.

People with ID have differing needs based on the range of their IQ; the person's ability to make informed choices is often diverse. The existence of co-morbidities differs related to the degree and presence of brain damage. One notable difference to this rule is that clinicians will assess and treat SME differently because it is not co-morbid to ID and is treated instead for the underlying SCNIA mutation.

When developing a care plan for an individual with ID and epilepsy, care and attention should be paid to the increased risk of adverse cognitive and behavioural effects of AED

treatment [5]. The UK recommendations, however, on choice and regular monitoring are no different for individuals with ID as in the general population [5-6]. There is little evidence to inform specific management [2], apart from some recommendations' surrounding consultation length and risk assessment around SUDEP [7]. This is despite there being many syndromes associated with epilepsy and ID, a small number of common ones which are listed in table 1 and discussed further in section 2 [8].

Some syndromes which are linked with development of ID such as Landau-Kleffner syndrome, Lennox Gastaut, Dravet, and West syndrome though associated with treatment resistant epilepsy and drug sensitivity have been more extensively investigated and evidence based guidelines do exist in individual syndrome cases. This is, however, more the exception then the rule for majority of people who have ID and epilepsy.

There is concern regarding a lack of research and insight into epilepsy and general comorbidities among individuals with an ID. Here we review the safety of prescribing AEDs in people with ID and identify the availability and quality of evidence in this area. The findings were examined from three perspectives –

1. AED side effects relating to behavioural, psychiatric and other co-morbidities and impact in people with ID.
2. Current practice of AED prescribing in relevant co-morbidities commonly associated with epilepsy and ID including recognised epilepsy syndromes
3. The evidence base of individual AEDs in the ID population

A literature review based on PRISMA guidelines was undertaken. Please see supplementary information 1 for more information on search strategy. PubMed/Medline, EMBASE, PsychINFO and Google-scholar were used to identify current evidence base of commonly used AEDs for prescribing in people with epilepsy and ID, PDD and genetic syndromes specifically associated with epilepsy, ID and or PDD.

The search returned 224,817 items. The three stage review of the items resulted in 43 items being included for analysis. The remaining 224, 772 were excluded due to small sample size or irrelevance. Of the 43, 17 were systematic reviews, 16 cohort studies, 6 randomised control trials and 4 case control studies. Of these 43 papers, 30 (see supplementary information 2) were found relevant for the study. .

AEDs side effects of behavioural, psychiatric and other co-morbidities in people with ID

There is substantial evidence to link AEDs with psychiatric and physical co-morbidities in individuals with epilepsy as well as an ID.

One descriptive review of 68 articles examined the neuropsychological effects of epilepsy and AEDs amongst the general population [9]. It has been highlighted that epilepsy itself has a number of cognitive and behavioural challenges often associated to an underlying neuropathology. The neuropsychological impact of AED treatment must be examined on an individual basis. It is emphasised that whilst some AEDs can impair neuropsychological functioning, improvement in seizure control could also result in improvement in the associated cognitive and behavioural consequences of epilepsy [9].

The association between epilepsy, ID and co-morbid psychopathology remains an area of limited understanding. Co-morbid psychopathology was investigated amongst two hundred and fifty people using an administrative database. One third of individuals were found to meet criteria for possible psychiatric disorder, particularly affective/neurotic disorder. The study identified that intellectual, sensory, motor disability and side effects of AEDs contributed significantly to explaining individual behavioural problems [10]. In a further comparative study, people with ID and epilepsy (N=156) were compared to those with ID and no epilepsy diagnosis (N=596) whereby the presence of epilepsy was found not to be associated with an increased likelihood of co-morbid psychopathology [11].

The SANAD trial provides the most accurate comparison in people without ID for side effect profile and quality of life [12]. It was an unblinded randomised control trial of a large number of people randomised to a number of AEDs. People with newly diagnosed epilepsy were randomly assigned to receive carbamazepine, gabapentin, lamotrigine, sodium valproate, oxcarbazepine or topiramate. Around 50% of individuals reported an adverse event at some point although differences across AEDs were not considered significant. Clinical anxiety was reduced in people treated with topiramate when compared with carbamazepine and gabapentin. Reduced risk of depression was also identified in people treated with lamotrigine when compared with other AEDs. No similar study has been conducted in people with ID and epilepsy. No specific evidence is available to help ascertain if certain AEDs perform better or worse from a side effect point of view in the population with ID as compared to general population.

1. **The use of AEDs in specific epilepsy syndromes associated with ID**

The term epilepsy syndromes refer to severe brain disorders which usually present at an early age. The heterogeneity of different syndromes associated with epilepsy and co-morbid ID makes it difficult to group them together.

Many epilepsy syndromes are closely associated with the development of ID due to progressive cognitive and behaviour decline. Exceptions such as Juvenile Myoclonic Epilepsy (JME) exist which has onset in adolescence and no obvious cognitive decline or association with ID.

Seizures associated with specific epilepsy syndromes are commonly pleomorphic and intractable. People may also present with progressive cognitive, behavioural and neurological deficits [13]. Epilepsy syndromes tend to be defined based upon seizure type, topographic origin of seizures, related symptoms and age of onset. Various epilepsy syndromes are recognised but most have been poorly studied especially with regard to the role of AEDs.

There is, however, more knowledge of AED management in Dravet syndrome and West's syndrome which present with severe childhood epilepsy usually with mild to severe ID [13].

AED treatment for epileptic syndromes can be associated with exacerbation of seizures and can trigger new seizure types [14]. For example, in an evaluation of the efficacy of lamotrigine amongst people with Dravet, the drug seemed to have caused an aggravation of seizures in most participating people [15].

Lennox-Gastaut syndrome (LGS) is a severe childhood epilepsy syndrome and has one of the highest incidence with estimated prevalence around 15/100,000. LGS represents 5-10% of all people with epilepsy and as a result is one of the most studied epileptic encepalophathies. It usually presents with multiple seizure types which are treatment resistant and associated with severe ID. Dose-related drug toxicity is common and freedom from seizures is extremely rare [16]. Of all AEDs, rufinamide has been suggested to be of the most benefit in this group when compared to felbamate, lamotrigine and topiramate [17].

2. Evidence of use of specific AEDs in ID population

Specific evidence of individual AEDs in people with ID is generally poor and where available is discussed below. There is also a significant lack of evidence of individual AEDs as applied to the different subsets of ID.

A popular choice is Benzodiazepines (e.g. clonazepam, clobazam, clonazepam, diazepam & midazolam) which are used as both rescue medication and as an effective add-on treatment in refractory epilepsy, especially common in people with an ID [18]. Clobazam in particular is recognised as being especially useful as intermittent rescue treatment, given in short courses to break up clusters of seizures or to provide short-term break to help develop more robust treatment strategies. Clobazam is considered appropriate to use regularly as second line or adjunct therapy for all major seizure types and especially of particular value in refractory epilepsy. Tolerance is a major issue particularly in ID populations although it is speculated that around 30% PWE on clobazam could continue without encountering the long term tolerance. The potential negatives of tolerance include the distress of changing medication and the need to reduce slowly if tolerant in addition to the other side effects which one encounters with benzodiazepines as a group. The other risk is that significant numbers of PWE and ID find themselves on various benzodiazepines to handle behaviour, mood or anxiety. There needs to be awareness of the overall 'benzodiazepine load' by clinicians prescribing and monitoring Clobazam for seizures.

Commented [RS1]: **Clobazam: A Safe, Efficacious, and Newly Rediscovered Therapeutic for Epilepsy**
1.Angela C. Gauthier[1,*] and
2.Richard H. Mattson[2]
CNS Neuroscience & Therapeutics
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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 [18]. There are no definitive studies or guidelines to guide treatment using this group of drugs. No studies were identified in ID populations which examined the popular belief that benzodiazepines are more likely to cause paradoxical agitation and severe hypersialorrhea.

Gabapentin and lamotrigine are broadly considered safe treatment for epilepsy in people with an ID. The efficacy and safety of gabapentin and lamotrigine was assessed in a randomised open-label study of 109 adults with ID and treatment-resistant epilepsy [19]. Safety and tolerability were assessed using adverse event reports. The overall incidence of adverse events was similar across the treatment groups with 62% reporting an adverse event on gabapentin and 50% on the lamotrigine group. Ten percent reported serious adverse events on the gabapentin group and 11% on lamotrigine. This was the first reported randomised trial for add-on AED medication in people with epilepsy and an ID. It concluded that both drugs were effective AED treatment options for seizure control and without causing significant worsening of behaviour as evidenced using the Whelan and Speake scale [19].

A case review of the first 51 people with LGS prescribed vigabatrin, lamotrigine and 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 [20]. Vigabatrin had previously been associated with the development of visual field defects but this report does not comment upon this. The use of vigabatrin amongst peoples with an ID raise serious ethical concerns as the BNF states that all prescribed vigabatrin must be made fully aware of the risk of visual field defects and how to report these to their physician.

The efficacy of lamotrigine was evaluated in a case review of 44 people with severe ID (IQ <20), developmental disabilities and epilepsy in institutionalised care. An overall seizure frequency reduction of >75% was reported in a third but 21% had had an increase in seizures. Few adverse events were reported apart from two individuals who had gastrointestinal symptoms which led to discontinuation. The report concluded that Lamotrigine was well-tolerated amongst those with an ID and is effective in seizure management in treatment-resistant epilepsy though 35% experienced no major improvement or a worsening of seizures [21].

A retrospective case series evaluated the outcomes for 25 adults with ID and epilepsy being treated with lamotrigine. About a third was reported to have had >50% seizure reduction but none became seizure free. About a third had side-effects and a quarter had an increase in seizures, particularly if lamotrigine was prescribed at higher doses. This led to the recommendation that larger scale evaluations are needed to understand the use of lamotrigine in people with ID and refractory epilepsy in order to understand its safety and efficacy profile [22].

At present it is advised that for people with an ID, especially those susceptible to balance problems not to be prescribed phenytoin. It is also not recommended for long term use as it can lead to marked cognitive impairment or symptoms and signs of cerebella disease [23]. Preventing phenytoin intoxication and subsequent phenytoin-induced encephalopathy remains dependent upon very careful monitoring of people and frequent monitoring of drug levels [23]. This would prove difficult in people with ID given their distress potential to recurrent venepuncture and difficulties to fully comprehend the need for monitoring. The available literature highlights the complexity of using phenytoin in ID populations and the lack of systematic evaluation.

A randomised double-blind, placebo-control trial using topiramate as an adjunct therapy in adults with both epilepsy and an ID looked to evaluate the impact of topiramate upon seizure severity and quality of life [25]. The study was completed by 57 participants with 28 and 29 in the topiramate and placebo groups. An overall reduction of 32% in seizure frequency was noted in the topiramate group compared with a 1% rate in the placebo group. Topiramate was found to be generally well tolerated and did not have a negative impact upon behaviour. This study concluded that topiramate reduced seizure rates in patients with epilepsy and ID without compromising quality of life.

Studies of tolerability of AEDs such as ethosuximide, carbamazepine, eslicarbamazepine, retigabine, zonisamide, levetiracetam and Perampanel in ID populations are extremely limited. To date, the tolerability and efficacy of these AEDs has not been evaluated in any suitable fashion amongst ID populations.

A problem uncommonly encountered in ID populations is of pregnancy when on AEDs. A recent study identified 217 pregnancies occurring to mothers with recorded ID of a total of 245 007 births in Oxford (population: 850,000) between 1970-1989. No major differences were seen in offspring of mothers with ID. .

Commented [RS2]: **Childbirth in women with intellectual disability: characteristics of their pregnancies and outcomes in an archived epidemiological dataset**
1.A. D. Goldacre[1],
2.R. Gray[2] and
3.M. J
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There is no studies which have looked at teratogenic effects of AEDs specifically in mothers with ID and epilepsy. It would be expected that the impact of AEDs on pregnancy and their children would be no different in mothers with ID as the general population. There could be, however, additional confounders such as genetic disorders to which the foetus might be more vulnerable to. Given the significantly low numbers expected of mother with ID on AEDs (statistically less than 1/year for 1 million population) there would an expectation that such a pregnancy and post birth would be managed with highest levels of monitoring and surveillance. **Conclusion**

Up until the early 1990s six major drugs existed in the treatment of epilepsy. By 2004 10 new AEDs were made available in the UK. Currently with the further inclusion of five more drugs the available number of AEDs has grown to over 20.

There are a number of concerns posed by these medications ranging from teratogenic concerns to negative impact upon cognitive function to worsening behaviour, all which can have an effect upon quality of life of the individual and carers [26].

Whilst treatment guidelines have suggested that the newer AEDs tend to be better tolerated and affect cognitive functioning to a lesser degree than older AED options [2] the evidence base applied to people with ID as shown by this review is currently extremely weak.

Identifying adverse effects to treatment is extremely challenging in individuals with an ID and epilepsy due to the presence of complex co-morbidities and often profound communication barriers [2]. The available literature demonstrates that whilst treatments can be very effective against seizures, individuals with an ID can respond with significantly more adverse behavioural, physical and psychiatric reactions than in the general population.

An accurate and standardised measure of seizure rate, severity and side effect profile would directly address the issues highlighted in the paper but is a factor currently lacking in the clinical care of individuals with an ID and epilepsy due to a lack of satisfactory evidence base.

UK guidelines recommend that a new antiepileptic drug should only be considered if there is no proven benefit from the old drug, previous negative experiences or pregnancy [6]. As people with ID are over represented in the treatment resistant population a suitable evidence base for prescribing AEDs in this population is vital. There is a significant need for new drugs to be assessed to show long term efficacy, and to clearly assess the effect upon a person's quality of life and tolerability in a standardised manner [1]. A summary of current good practice for use by neurologists in clinical practice when attending to a routine PWE with ID has been proposed in supplementary information 3.

The UK register for AEDs in ID populations has been established for 10 months and has been investigating Perampanel as the pilot compound. Study sites are currently recruiting with 60 people currently registered from Cornwall, UK. Early results do not indicate a significant difference in discontinuation of perampanel treatment based upon degree and nature of ID a number of significant adverse effects have been reported which do indicate a difference in response across ID and general populations.

Table 1: Common ID Syndromes associated with epilepsy

ID Syndrome	Percentage of Patients Diagnosed With Epilepsy
Autism	30% [2]
Autism with severe intellectual disability and cerebral palsy	67% [9]
Degenerative disorders	70% [9]
Rett syndrome	70-90% [10]

Appendix 1: Full Search Terms and Elimination Procedure

PubMed/Medline, EMBASE (neuroscience, pharmacology,medicine), PsychINFO and Google-scholar were searched. The search was divided into two components. The first component included the following keywords: Antiepileptic, antiepileptic drugs, anti-epileptic, Phenytoin, Phenobarbital, Benzodiazepines, (Clonazepam, Clobazam, Lorazepam, Diazepam, Midazolam, Carbamazepine, Oxcarbamazepine, Eslicarbamazepine, Sodium Valproate, Vigabatrin, Gabapentin, Pregabalin, Topiramate, Levetiracetam, Ethosuximide, Lamotrigine, Zonisamide, Lacosamide and Perampanel, intellectual disability, learning disability, mental retardation, complex needs, co-morbidity, additional handicaps, Dravet syndrome, Lennox-Gastaut syndrome, malignant epilepsy syndrome, complex epilepsy, Felbamate, Sulthiame, Acetazolamide, Rufinamide, Stiripentol, West's syndrome, autism, Landau-Kleffner syndrome, epileptic encephalopathies, epileptic encephalopathy, SUDEP. Only journals published between 1990 and January 2015 were included. The search was limited to English-language articles.

The second component included the following keywords: Intellectual disability, learning disability, mental retardation, complex needs, co-morbidity, additional handicaps, Dravet syndrome, Lennox-Gastaut syndrome, malignant epilepsy syndrome, complex epilepsy, West syndrome, autism, Landau-Kleffner syndrome, epileptic encephalopathies, and epileptic encephalopathy.

These two components were combined with the Boolean AND operator to create the overall search strategy: Dravet syndrome, Lennox-Gastaut syndrome, malignant epilepsy syndrome, complex epilepsy, West's syndrome, autism, Landau-Kleffner syndrome, epileptic encephalopathies, epileptic encephalopathy. Antiepileptic, antiepileptic drugs, Phenytoin, Phenobarbital, Benzodiazepines, Carbamazepine, Oxcarbamazepine, Eslicarbamazepine, Sodium Valproate, Vigabatrin, Gabapentin, Pregabalin, Topiramate, Levetiracetam, Ethoximide, Lamotrigine, Zonisamide, Lacosamide, Perampanel, SUDEP, Eslicarbamazepine, Benzodiazepines, Sulthiame.

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