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REVIEW ARTICLE

Patterns of antiseizure medications prescribing in people with intellectual disability and epilepsy: A narrative review and analysis

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People with intellectual disabilities (PwID) have a bidirectional relationship with epilepsy. Nearly 25% of PwID have seizures and 30% people with epilepsy are thought to have a significant intellectual impairment. Furthermore, 70% of PwID are thought to have treatment-resistant epilepsy. In the United Kingdom, antiseizure medications (ASMs) are the second most widely prescribed psychotropic agent for PwID. However, it is unclear what the current evidence and patterns is on current prescribing of ASMs, including when and how a case is made to withdraw them. A narrative review along with an analysis of large-scale NHS Digital published data (2015–2020) on several aspects of ASM prescribing by general practices for PwID was undertaken. The review results and data analysis are consolidated and presented as 11 themes to provide a comprehensive overview of the study topic. Recent studies estimate that one-third and one-fifth of PwID are prescribed ASMs. A history of epilepsy is seen as the primary prescribing reason; however, often it is a legacy, and the indication is no longer clear. The proportion receiving ASMs continues to rise with age. This pattern of use does not correlate well with seizure onset. There are limited data on de-prescribing ASMs in PwID. The study population heterogeneity, associated polypharmacy, multimorbidity and higher sudden unexpected death in epilepsy risks are outlined. Suggestions are made from available evidence for improving prescribing practices for PwID and seizures, and key areas for further research in this complex clinical area are outlined.

KEYWORDS

antiseizure medications, intellectual disability, polypharmacy

1 | INTRODUCTION

Antiseizure medications (ASMs) are diverse. In addition to their value in the treatment of epilepsy they are prescribed for several psychiatric and neurological conditions. The licensed indications include epilepsy, trigeminal neuralgia, prophylaxis of bipolar disorder, adjunct in acute alcohol withdrawal, migraine prophylaxis and mania.¹

The prevalence of epilepsy in people with intellectual disabilities (PwID) is estimated to be between 20% and 25%.² PwID and epilepsy have higher rates of physical and psychiatric comorbidity, are more likely to be prescribed multiple psychotropic medications, experience neuropsychiatric side effects of medications, and suffer higher levels of premature mortality including sudden unexpected death in epilepsy (SUDEP).³

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ASMs are psychotropic agents and the interrelationship between seizures and behaviour when prescribed ASMs can be complex.⁴ The lifetime risk of psychiatric disorders in PwID appears to be considerably higher than in people without intellectual disabilities (ID).⁵ Furthermore, in PwID and epilepsy, the risk of mental illness was reported as being up to seven times higher over a year when compared to those with ID alone.⁶

There is growing recognition of polypharmacy (defined as greater than five medications prescribed) and the need to counter it in PwID.^{7,8} In England, the National Health Service (NHS) launched a campaign to stop overmedication in PwID, autism or both (STOMP).⁹ The principal focus was on antipsychotic and antidepressant use not indicated by suitable illnesses. However, there has been no attempt to investigate the extent of use of ASMs in PwID and whether they are overprescribed.

This study looks at the published literature along with analysis of publicly available NHS Digital data on national prescribing patterns in the United Kingdom with a view to quantifying the extent of ASM prescribing in PwID.

2 | METHODOLOGY

A narrative approach was conducted to combine information from NHS Digital data and a database search.

2.1 | Review

The review reporting was guided by the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement (Supporting Information S1).

2.1.1 | Scope

The topic of interest was understanding current literature on prescribing and reviewing ASMs in PwID and epilepsy. The search terms and designs (Supporting Information S2) were established to identify papers that were focused on prescribing ASM in PwID and evidence-based ASM withdrawal studies. There were no limits on dates but only studies published in English were considered.

2.1.2 | Searching

The search strategy was designed and implemented by an Information Specialist using Embase (Ovid), Medline (Ovid), CINAHL (EBSCO) and PsychINFO (ProQUEST) databases. The search strategy used a combination of text words and subject headings, combined with Boolean operators, resulting in 433 references being identified and added to an EndNote library.

2.1.3 | Full-text screening

The full text of all selected papers' references, including the potentially relevant ones, was retrieved for closer examination.

We erred on the side of inclusion if there was any doubt about its inclusion to ensure no potentially relevant papers were missed. The inclusion criteria were then applied against the full-text version of the papers by two reviewers. The inclusion criteria included papers which primarily discussed ASM prescribing patterns in PwID. Papers which also generally had influence on prescribing applicable to PwID were also included. Disagreements regarding eligibility of studies was resolved by discussion and consensus within the project team.

Key data related to the study topic was extracted from the included papers, which involved year of study, design, study objectives, target population, method/s tested, outcomes reported, country of study/studies and results. Data extraction was performed by two reviewers and reviewed by the project team.

2.2 | NHS Digital data extraction

The Department of Health in England and NHS England collect routine clinical data so they can learn about specific areas of policy interest and measure the progress of policy initiatives. These national datasets collect information from care records, systems and organizations on specific areas of health and care. This is used to inform policy and monitor and improve care. Most studies of ASM use in PwID are based on data generated by General Practice (GP) prescribing systems. The overall proportion of patients registered with GPs varied over the 5 years of the study from 56.2% to 60.3%. However, coverage varied greatly between the current seven NHS regions, ranging from 19.5% to 87.8% in the most recent year.

In January 2021 NHS Digital published data on several aspects of psychotropic and ASM prescribing by general practices for people identified as having ID along with comparison data for the rest of the registered population.¹³ The data are on a large scale and document the years 2015/2016 to 2019/2020. They were collected as an addition to the dataset called "The Health and Care of People with Learning Disabilities" which was introduced to support STOMP (Stopping Over-Medication of People with a Learning Disability, Autism or Both).⁹ Two experts in big data and the subject of medication prescribing in intellectual disabilities, an epidemiologist and a pharmacist respectively, reviewed the dataset to extract key findings relevant to the study topic.

3 | RESULTS

The range of study designs included ranged from randomized control trial (RCT) studies through to other published original research excluding case series and case studies in peer reviewed index-linked

journals. Studies conducted within the United Kingdom and from other countries with similar characteristics to the UK where these are robust in design and content were included.

3.1 | Title and abstract screening

Before starting the title and abstract screening, 31 duplicates were removed from the working reference list, which brought the number down to 402 references. One author completed screening according to the selection criteria. This concluded with the identification of 37 references. The list was then shared with another reviewer from the team who undertook another screening. Rayyan was used during this screening stage. All 37 articles were exported from Rayyan to Excel. The full-text screening reduced 37 papers to 22. These 22 included 12 papers from the databases and 10 from other sources. The other sources were from citation searching ($n = 4$) and reports from influential stakeholder organizations such as the International League against Epilepsy (ILAE), the Royal College of Psychiatrists and NHS England ($n = 6$).

A narrative thematic approach is used to summarize the findings. Findings include evidence drawn from both the literature search and the dataset analysis. Eleven themes were identified. Supporting Information S3 provides the 22 papers selected, their origin (i.e., from database search, citation or other source) and the specific theme/s where they have been utilized. The source of the evidence i.e., if from the review (section A) or from the NHS Digital data extraction (section B) is indicated.

3.2 | Theme 1—Prevalence of ASMs in PwID

Most early studies of ASM prescribing in PwID were based on data from institutional cohorts of patients or from specialized epilepsy clinics. They typically reported 20%–30% of the ID population receiving ASMs. Table 1 shows the results for review (section A) of the recent studies in the last 5 years outlining the prevalence of ASM prescribing for PwID in the UK. Roughly a fifth to a third of PwID appear to be on ASMs. Table 2 shows the results of the NHS digital extraction (section B) 2020–2021 data of the rate of ASM prescribing for PwID for those with epilepsy. The proportion of PwID receiving ASMs continues to rise throughout the age bands for each year between 2015/2016 and 2019/2020.

The review (section A) suggests that a gradual rise in ASM prescribing with increasing age is a common finding of most other recent studies. A Public Health England (PHE) study from 2015 found the rate of ASM prescribing in those aged under 18 was 10.2% but this rose to 17.7% at ages 18–24 and more than 20% in older ages.¹¹ A later PHE study from 2019 found ASMs were prescribed to 17.3% at ages 18–24 and 22.7% at ages 25–44.¹² They also found that between 2011 and 2017 ASM prescribing rates in older groups of PwID rose from 25.4% to 30.9% in people aged 45–64 and from 20.6% to 26.8% in people aged 65 and older.

TABLE 1 Rate of antiseizure medication (ASM) prescribing for PwID.

Study	Rate of ASM prescribing	Details of population studied
Henderson et al. ¹⁰ (Scotland)	In 2002, 28% of attenders with ID received ASMs, and although this was fewer in 2014 (26%), in those PwID common to both the 2002 and 2014 snapshot surveys the prescribing of ASMs had increased from 25% to 31% over the 12-year period.	Based on clinic data
Glover et al. ¹¹ (UK)	20.6% of PwID prescribed ASMs.	Data from the THIN GP based system
Mehta and Glover ¹² (UK)	23.3% of PwID prescribed ASMs.	Data from the THIN GP based system
NHS Digital ¹³ (2019–20 data) (England)	16.7% of PwID who had a diagnosis of epilepsy and are currently on an ASM. 5.6% of PwID without an active diagnosis of epilepsy are being treated with ASMs	56.6% of General Practices for 2019–20 data

TABLE 2 The age-related rate of ASM prescribing for PwID and epilepsy.

	On ASMs with epilepsy	% ID
0–9	595	6.10
10–17	2040	9.93
18–24	3462	13.33
25–34	5978	16.91
35–44	4653	20.10
45–54	4694	21.49
55–64	4435	21.75
65–74	1968	19.63
≥75	522	13.47

Note: Data from NHS Digital.

An Irish 2018 study of a nationally representative sample of 753 PwID aged between 41 and 90 years, showed 38.9% received ASMs, and 30.6% had a diagnosis of epilepsy.¹³ Of those with epilepsy, 90.9% reported concurrent use of ASMs.

Multiple ASM use was seen to increase with age, with 43.3% for adults with PwID being on multiple ASMs as compared to 27.9% for children and young people.¹² The PHE study of 2015 found multiple psychotropic prescribing involving more than one class of

psychotropic was also more common in those over 18 years of age.¹¹ Of those under 18 years of age prescribed ASMs, 79.8% received only one psychotropic medication (including ASMs) but in adults the rate had fallen to 52.2% with significantly greater co-prescribing with anti-psychotics (females 25.2% [23–27.6], males 28.5% [26.5–30.7]) and antidepressants (females 23.3% [21.2–25.6], males 15.8% [14.1–17.5]). The PHE study of 2015 found there was no consistent gender difference in the use of ASMs and that most prescribing, almost 100%, was long term.¹¹ Although the use of ASMs is diverse, the majority of ASM prescribing in PwID is for those with a history of epilepsy.

3.3 | Theme 2—The use of ASMs in PwID and epilepsy

The review (section A) identified very few studies assessing pharmacological interventions for PwID with epilepsy.¹⁴ A 2015 Cochrane review broadly supports the use of ASMs to reduce seizure frequency in PwID with refractory epilepsy.¹⁵ The quality of evidence identified by this review is low to moderate. The studies were heterogeneous in terms of type of ASM and reported on different outcomes.

3.4 | Theme 3—Prevalence and characteristics of epilepsy in PwID

Our study review (section A) identified a 2015 systematic review aimed to provide a summary of prevalence studies for epilepsy in PwID and estimated prevalence based on a meta-analysis.² A total of 48 studies were included in the tabulation and 46 studies were included in their meta-analysis. The pooled estimate from 38 studies of epilepsy in PwID was 22.2% (95% CI 19.6–25.1). The authors found prevalence of epilepsy increased with severity of ID. Two regional English studies showed that multiple seizure types are a common presentation, and that for three-quarters of PwID and epilepsy the seizures remain refractory to treatment.^{16,17}

3.5 | Theme 4—The natural history of epileptic seizures

The review (section A) identified supportive studies. The natural history of epileptic seizures in the general population shows that the greatest incidence of new cases appears between the ages of 1 and 4 years.¹⁸ After the age of 18 years the incidence of new cases remains low, only to rise again after the age of 65.

A Swedish sample of 299 cases with epilepsy and ID showed the prevalence of epilepsy remaining constant during much of the period from 20 to 60 years of age.¹⁹

However, a 2022 retrospective multi-centre cohort study of 904 adults living in the United Kingdom across 10 secondary care centres suggested that the pattern in PwID may be different.²⁰ They

reported some with a later onset of seizures and separated the ID population into two distinct groups and outlined the differences in characteristics between the two (Table 3).

A study of an ID population living in institutional care in Norway supported this finding of older onset seizures; they found 29% suffered their first seizure after the age of 20.²¹

3.6 | Theme 5—Seizure control

For many PwID, their epilepsy remains refractory to treatment. However, a significant proportion become seizure free, and this proportion increases with age as identified by our review (section A) (Table 4).

In 2022 a multicentre observational study of 904 adults with ID and epilepsy living in the United Kingdom reported that 32% had no seizure in the last 12 months and 13% had not had a seizure in the last 5 years.²⁰

Data on the recording of seizures of PwID and epilepsy is one of the themes of the 2021 data from NHS Digital (section B).²⁶ The proportion recorded as being seizure free for 12 months or more using NHS Digital data was 45.3% for PwID and 61.8% for those without ID.¹⁰ Data on the proportion of those seizure free at 1 year who continue to remain seizure free at 2, 5 or more years is not available. The likelihood of prevalence of seizure freedom in PwID for at least 1 year increased with age (Table 5).

3.7 | Theme 6—Deprescribing ASMs originally prescribed for epilepsy

Various reviews on the subject were identified by our review section (section A). A 2019 review of the protocols surrounding stopping ASMs in children recommend it is necessary to consider the following questions: why stop, when to stop, for which patients to stop and how to discontinue treatment.²⁷ They recommended ASMs are stopped when they are no longer necessary and when there are concerns related to toxicity/side effects (behavioural, cognitive and

TABLE 3 The age-related numbers of adults with ID diagnosed with epilepsy within the previous 5 years.

Age category	The numbers with epilepsy	The numbers diagnosed with epilepsy <5 years ago
18–24	154	17
25–34	246	11
35–44	178	7
45–54	151	4
55–64	129	6
65–74	37	1
≥75	17	2
Total adults	912	48

TABLE 4 Studies that detail the rate of seizure-free individuals in varied populations of people with ID.

Reference	Population studied	Proportion seizure free
Goulden et al. ²²	Aberdeen. Prospectively identified cohort of 221 children with ID born between 1951 and 1955	By age 22 years, 39% had achieved 5-year seizure-free remission, including 56% of ID children without associated disability, 47% of ID children with Cerebral Palsy, and 11% of ID children with a postnatal injury.
Forsgren et al. ¹⁹	Sweden. All adults and children with ID in one county on a prevalence day. Register of neurology and paediatric departments	No seizures in the 12 months prior to census day in 32%
Beckung and Uvebrant ²³	Sweden. 217 children and adolescents	29% seizure free in previous year
Brodtkorb ²¹	Norway. 63 institutional adults	36% seizure free for three years
Collacott et al. ²⁴	Leicestershire. 215 adults	22% seizure free initially but increased to 41% over period of review
Branford et al. ¹⁶	Leicestershire. Cohort of 138 patients common to 1985 and 1997	No seizures for 5 years – 24% (1985) – 20% (1997) No seizures for 3–5 years – 18% (1985) – 9% (1997)
McGrother et al. ¹⁷	Leicestershire. 620 adults	23.2% having no seizures (period unspecified)
Matthews et al. ²⁵	UK. 318 adults from 40 general practices	26% seizure free (period unspecified) Mild ID 49% Moderate ID 32% Severe/profound ID 24%
O'Dwyer et al. ¹³	Irish Longitudinal Study on Aging, a nationally representative sample of 753 persons with ID aged between 41 and 90 years	Of those with ASMs polytherapy ($n = 103$), 29.5% (28) reported being seizure free for the previous 2 years

chronic side effects). It is possible to stop ASMs in 65%–85% of patients if ongoing remission is achieved.

A Cochrane review examining discontinuing ASMs in children supported waiting for at least two seizure-free years before discontinuing the ASM, particularly if individuals have an abnormal EEG or partial seizures, or both.²⁸ They concluded that there is insufficient evidence to establish when to withdraw ASMs in children with

generalized seizures or to guide the timing of withdrawal in seizure-free adults.

A 1998 review supported attempts to discontinue ASMs in PwID.²⁹ The authors stated that later onset of seizures, a normal EEG, monotherapy and complete control of seizures suggested the likelihood of a better outcome. They suggested that for those with partial seizures but no genetic features and 2–4 years seizure free, the outcome from withdrawal of ASMs was good.

A 1994 study from Norway of institutionalized PwID followed up 23 patients who were seizure free for 3 years and discontinued ASMs.²¹ In this study, 61% remained seizure free for 2 years post withdrawal. Neither the degree of ID, the presence of cerebral palsy nor EEG abnormalities were major determinants of outcome; however, epilepsy before the age of 2 was. When to embark on the withdrawal of ASMs prescribed for PwID whose epilepsy is in remission remains a highly debated and contentious issue.

3.8 | Theme 7—Impact of ASMs on neuropsychological functioning

The study review section (section A) identified various studies on this theme. A 2007 study looked at the influence of major ASMs on neuropsychological function following a randomized, double-blind, placebo-controlled withdrawal of seizure-free non-ID epilepsy patients on monotherapy.³⁰ The major findings were that, in subjects with therapeutic drug levels at baseline, ASM withdrawal was associated with significant improvement in verbal fluency and executive functioning.

In another study seizure-free epilepsy patients without ID, on ASM monotherapy who tapered their medication were found to improve neuropsychological performance with a relative risk of seizure relapse of 2.46, compared to those continuing therapy.³¹ Patients were randomized to ASM withdrawal ($n = 79$) and no withdrawal ($n = 81$) groups. The examination programme included clinical neurological examinations, neuropsychological testing, EEG recordings, cerebral MRI and assessments of health-related quality of life (HRQL). Follow-up data on seizure relapse were also collected beyond the 12-month study period (median 47 months). Seizure relapse at 12 months occurred in 15% of the withdrawal group and 7% of the nonwithdrawal group. At 41 months off medication, seizure relapse rates were 27%. A normal result to all 15 neuropsychological tests increased significantly from 11% to 28% post withdrawal, with no significant effects of withdrawal on quality of life and EEG. Despite this study, the American Academy of Neurology 2021 guidance update stated that in adults who are seizure free, ASM weaning may not change quality of life.³²

An observational study of patient records from North America of 4085 adult patients (18+ years) newly started on an ASM regimen compared the psychiatric and behavioural side effect profiles of older and newer ASMs in a large specialty practice-based sample of patients diagnosed with epilepsy.³³ They found that psychiatric and behavioural side effects occurred in 17.2% of patients and led to

TABLE 5 The number of adults with ID and epilepsy 1 year seizure free in England.

Age category	The numbers of people on GP register with ID as having epilepsy and on ASMs in this age category ^a	Rate of people with ID on GP records as having epilepsy and on ASMs (%) (95% CI)	Rate of people with ID and epilepsy at least 1 year seizure free (%) (95% CI)	No of people with ID seizure free for 1 year ^a (extrapolated to 100%)
18–24	11 250	13.3 (12.9–13.7)	34.4 (31.6–37.3)	3870 (6789)
25–34	22 200	16.9 (16.5–17.3)	40.8 (38.7–43.0)	9058 (15 891)
35–44	26 571	20.1 (19.5–20.6)	43.4 (41.0–45.8)	11 531 (20 229)
45–54	32 904	21.5 (20.9–22.0)	48.6 (46.2–51.1)	15 991 (28 054)
55–64	33 711	21.8 (21.2–22.3)	50.1 (47.6–52.6)	16 929 (29 700)
65–74	27 140	19.6 (18.4–20.4)	55.9 (51.9–59.8)	15 171 (26 615)
≥75	24 175	13.5 (12.4–14.5)	69.1 (61.3–75.9)	16 705 (29 307)
Total				89 255 (156 157)

^a57% of GP practices in England.

intolerability in 13.8% of patients. A history of psychiatric condition(s), secondary generalized seizures, absence seizures and intractable epilepsy were associated with increased incidence of psychiatric and behavioural side effects.

Levetiracetam had the greatest psychiatric and behavioural side effects rate (22.1%). This was statistically significant when compared with the aggregate of the other ASMs ($P < 0.001$, RR = 6.87). Levetiracetam was also significantly ($P < 0.001$) associated with higher intolerability rate (17.7%), dose decreased rate (9.4%), and complete cessation rate (8.3%), when compared with the aggregate of the other ASMs. Valproate was associated with lower psychiatric and behavioural side effects when compared individually with the aggregate of other ASMs. All other ASMs were found to have intermediate rates. There are no equivalent studies of the ID population.

3.9 | Theme 8—What factors are associated with poor prognosis following ASM withdrawal?

There are many studies on the factors associated with prognosis following ASM withdrawal. However, most relate to the general population and to children. Table 6 summarizes the factors associated with prognosis following ASM withdrawal in the general population extracted from two studies identified from our review (section A). It includes the 2013 Italian League Against Epilepsy evidence-based guidelines³⁴ and a 2017 meta-analysis using data from 45 studies with 7082 patients to develop an individualized prediction model of seizure recurrence and long-term outcomes after withdrawal of ASMs in seizure-free patients.³⁵ However, no similar guidance exists specifically for PwID with epilepsy.

3.10 | Theme 9—Stopping ASMs prescribed for PwID

Little evidence was found on this by the review (section A).

3.10.1 | How to withdraw ASMs

A 2006 Cochrane review attempted to study rapid vs. slow withdrawal of ASMs.³⁶ Only one small study was identified, and they were unable to derive any reliable conclusions regarding the optimal rate of tapering of ASMs. They were also unable to provide evidence about the effects of variables such as seizure types, its aetiology, ID, EEG abnormalities, presence of neurological deficits and other comorbidities on the rate of tapering. In the United Kingdom, the Royal College of Psychiatrists suggest a slow and gradual reduction.^{37,38}

3.10.2 | Withdrawal effects

It is widely thought that ASMs are not associated with withdrawal effects.³¹ Some are recommended as alternatives to assist with alcohol withdrawal. There are reports of a variety of symptoms upon withdrawal including headache, dizziness, stomach and gut problems, difficulties with memory, learning and thinking, sensory disturbances and general fatigue. Withdrawal of sodium valproate has been reported to cause fast heart rate, excessive sweating and tremor, which resolved within a few days.³⁹

3.11 | Theme 10—The case for stopping ASMs in PwID

In addition to the concerns outlined earlier, there are a few other considerations to actively promote stopping or reducing ASMs in PwID and epilepsy as supported by our review (section A).

3.11.1 | ASM drug interactions

Of all those PwID who died prematurely, the LeDeR reports (2018–2020) highlight that nearly 50% were prescribed ASMs.⁴⁰ The mean

TABLE 6 Summary of factors associated with good or poor outcome following ASM withdrawal.

Beghi et al. ³⁴	Lamberink et al. ³⁵
Italian League Against Epilepsy	Individualized prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: Independent predictors of seizure recurrence
Methodology: panel critically appraised 128 published reports	Methodology: a systematic review and individual participant data meta-analysis
Recommendations	Findings
In adults, ASMs might be discontinued after a minimum period of 2 years of seizure freedom. Shorter seizure-free periods are associated with a higher risk of relapse.	The common understanding that it is advisable to wait for at least 2 years is based on an artificial threshold and the rule should at least be complemented by adding that every added seizure-free year reduces the risk.
<p>Factors that enhance the risk of relapse include:</p> <ul style="list-style-type: none"> • abnormal EEG (including epileptiform abnormalities) at the time of treatment discontinuation • a documented aetiology of seizures (including ID, perinatal insults and abnormal neurologic examination) • partial seizures • an older age at disease onset 	<p>Factors that enhance the risk of relapse include:</p> <ul style="list-style-type: none"> • epileptiform abnormality on electroencephalogram (EEG) before withdrawal. EEG abnormalities were significantly associated with outcome, but in the absence of other predictive factors they only slightly increased the risks. EEG abnormalities alone should thus not prevent withdrawal of medication. • age at onset of epilepsy. The age at onset of epilepsy is an important predictor for seizure recurrence but not for long-term freedom from seizures. Its association with seizure recurrence is U-shaped, with an elevated risk at birth that falls to a nadir by about age 3–4 years when it begins to rise again until age 10 years and plateaus until age 25 years; subsequently, the risk continues to rise further with older ages of onset. • history of febrile seizures • number of seizures before remission • developmental delay
<p>The following should not influence the decision to stop treatment:</p> <ul style="list-style-type: none"> • female sex • family history of epilepsy • history of febrile seizures • disease length/severity • number and type of ASM taken 	<p>Factors not shown to enhance the risk of relapse:</p> <ul style="list-style-type: none"> • generalized tonic-clonic • multiple seizure type • febrile seizures • history of neo-natal seizures
Epilepsy syndromes should be always included in the decision process.	Absence of a self-limiting epilepsy syndrome.
<p>Slow (at least 6 months) ASM discontinuation should be encouraged. The duration of the tapering period should be tailored to the patient's needs and preference.</p> <p>Significant results in favour of longer tapering periods were obtained in four studies, one of them after adjusting for other factors.</p>	The failure of a previous attempt to withdraw from medication seizure recurrence after previous antiepileptic drug withdrawal is not related to the outcome of a second (or third) attempt.
<p>Patient discontinuing treatment should be followed for at least 2 years. The relapse rates were highest in the first 6 months after completion of treatment stop and decreased thereafter.</p>	
The decision to stop treatment should be discussed and shared with each patient, considering social and personal complications of a seizure relapse and the medical complications of chronic AED treatment	When counselling patients with the use of these prediction models, a physician should be aware of other factors such as fear. The social stigma around seizures and the quality of the patient's life are important considerations

(average) number of usual medications prescribed for this population was 6.2 (SD = 3.6, range 0–20) for people who died in 2018; 6.5 (SD = 3.6, range 0–21) in 2019; and 6.6 (SD = 3.6, range 0–24) in 2020. This thus raises the question of not only the potential burden of polypharmacy, especially of ASMs, on those who have died prematurely but suggests vulnerability to major and dangerous effects due to drug interactions.

3.11.2 | Bone impact

Epilepsy is recognized to be associated with significantly impaired bone health including osteoporosis and bone fractures, especially in PwID.⁴¹ A recent study on PwID and epilepsy who have been on a minimum of 2 years of ASMs has shown 66% to have osteopenia/osteoporosis changes and 90% to be vitamin D insufficient.⁴²

3.11.3 | PwID and epilepsy over 40s

Recent research has shown that PwID and epilepsy over the age of 40 have higher levels of clinical risk factors associated with multi-morbidity, potential iatrogenic harm and premature mortality with worse clinical oversight mechanisms compared to their younger peers.⁴³ There is recognized increased polypharmacy in this group. There is a need to actively reduce potential therapeutic harm.⁴⁴

3.12 | Theme 11—What are the potential issues to prevent withdrawal of ASMs prescribed for PwID and epilepsy?

3.12.1 | Seizure issues

Epilepsy is the most common long-term condition associated with premature mortality in PwID.^{40,45} The greatest hazard of a chronic condition resulting in premature mortality in PwID was associated with having epilepsy compared to not having epilepsy (HR 1.47; 95% CI 1.28, 1.69).⁴⁵ The most obvious reason to continue ASMs is the risk of relapse of seizures. PwID remain at high risk of recurrence of seizures even after many years of remission. Given the disproportionate prevalence of genetic and neurodevelopmental comorbidity there is always a concern of recurrence.⁴³ Improved and more routine genetic investigations might identify groups that are likely to remain vulnerable to seizures through their lifetime, for example those with epileptic encephalopathies. Similarly, there has been a significant dearth of bespoke evidence on ASM impact on seizures in PwID.¹⁴ At present, initiatives like the national Ep-ID research register in the United Kingdom is providing level 2 evidence on the use of bespoke molecules for treatment-resistant epilepsy in PwID.^{46–48}

3.12.2 | Biological factors

PwID are more vulnerable to health impact directly or indirectly influencing their seizures.^{43,49} Acute health conditions such as urinary tract infections and chest infections predispose to seizures. Issues such as sleep and altered bowel movements might be potential influencers. It is unclear for how many PwID long-standing ASMs provides a safety net and prevent emergent seizures.

3.12.3 | Psychological factors

There exists a bidirectional relationship between seizures and mental health. PwID and epilepsy are vulnerable to both and have higher prevalence to both sets of conditions than the general population and their peers with ID without epilepsy.⁵⁰ Alteration of the balance of one could negatively influence the other, precipitating a vicious cycle

which could impact significantly and negatively on the confidence and quality of life of PwID.^{51,52}

3.12.4 | Risk matters

A major concern would be the potential increased risk of SUDEP precipitated by ASM withdrawal. It is recognized that rates of SUDEP are high in those PwID and could be at least three times greater than those without ID.^{53,54} In addition, it is recognized that PwID and epilepsy are at increased risk of emergency department attendances and admissions than their peers without epilepsy or those without ID.⁵⁵

These risk vulnerabilities, compounded with the lack of ability of PwID to possibly comprehend and communicate the difficult choices involved, could be a deterrent to ASM reduction.

3.12.5 | Heterogeneity of PwID and epilepsy

There has been recent international guidance on how to withdraw ASMs in seizure-free people. However, there is no consideration of special populations, particularly PwID.³² As outlined in this paper, there are various factors which predispose, perpetuate and precipitate seizures in this population.

4 | DISCUSSION

4.1 | Decision making—“Who's going to bell the cat”?

PwID are recognized to have a range of cognitive and social deficits leading to them being classified into mild, moderate, severe and profound as per recognized international diagnostic systems such as the DSM V.^{56,57} The terms “mild”, “moderate”, “severe” and “profound” not only describe the severity of the condition but also give an estimate of their ability to manage daily routine tasks, inform and participate in day-to-day decisions and the support they might need to do so.

A significant challenge is for the individual PwID to make an informed personal decision based on all the various considerations of risk and benefit due to the innate cognitive and communication difficulties. This is further accentuated by the fact that the presence of seizures is more likely to cause a moderate to profound cognitive deficit as outlined by a prevalence study.² Their meta-analysis gave a pooled estimate for studies including all levels of intellectual disability as 22.2% (95% CI 19.6–25.0), whereas the estimate for studies classed as “less severe” was 7.3% (95% CI 4.5–11.6) and the estimate for “more severe” 41.6% (95% CI 32.1–51.8).

In such a situation, given the considerable risks of harm and relapse, decision making can be challenging for any patient or patient representative to make. This has contributed to further accumulation

of medication without prioritizing withdrawal generally for this group but particularly for ASMs.

4.1.1 | Carer matters

When PwID are supported by a family member or friend who is actively involved in the individual's life, there is scope to make proactive decisions. However, if in care, especially in later adulthood, it is unclear how and where the responsibility should sit and be realized. This leads to decision paralysis gravitating to a status quo in clinical appointments.⁴³

Other challenges include observer bias, i.e., of those reporting the seizures, education given to carers and available resources to support ASM optimisation.

4.2 | Guidance for adults with epilepsy and ID for whom ASM withdrawal should be considered

It is not possible to accurately calculate the number of PwID suitable for ASM withdrawal; however, there are considerable numbers for whom it should be given consideration. It is also difficult to know to what extent the guidelines developed for the general population are applicable to PwID. However, clinicians may wish to consider the following:

- Ideally the discussions relating to whether the PwID continues to require ASMs should occur while still under the care of children or adolescent services.
- At transfer to adult services, the details relating to the person's epilepsy should be available, including the suitability for withdrawal of ASMs.
- Once PwID enter an extended period of seizure freedom, their potential for ASM withdrawal should be assessed.
- Those seizure free for more than 5 years should be withdrawn from ASMs unless there are risk factors that make relapse a likely outcome.
- Similarly, those not having generalized seizures and being seizure free for a substantial period need to be considered for ASM withdrawal given the lower impact on well-being and seizure safety.

4.3 | Limitations

Data on the recording of seizures of PwID and epilepsy is one of the themes of the data from NHS Digital.⁸ GP practices had previously been incentivized via the Quality and Outcomes Framework (QOF) to record seizure frequency but are no longer required to do so, with the result that only 27.9% of those with ID and 19.6% of those who did hold current records. NHS Digital expressed caution in interpreting the data as the low and different proportion of people for whom a

seizure diary is recorded complicates interpretation of the pattern of recorded seizure-free years.

A limitation of using individual participant data from previously executed studies is that prognostic factors can be defined differently.³⁵ For the included variables, some variation in the measurement of developmental delay and the definition of epilepsy duration was noted. Another limitation was the quantification of long-term seizure freedom chosen in the analysis.

This paper focuses on the prescribing of ASMs for a defined indication of seizures and not behavioural and psychiatric indications in PwID. There is a recent analysis on ASM use in PwID for nonseizure management and the available NHS Digital data on national prescribing patterns in England.⁵⁸

This paper also does not include other neurodevelopmental conditions such as autism spectrum disorder or attention deficit hyperactive disorder, though both conditions are recognized to be significantly comorbid with both in ID and epilepsy.

5 | CONCLUSIONS

The proportion of PwID receiving ASMs rises with age for both those with a history of epilepsy and those without. This review focused on the use of ASMs prescribed for PwID with a current or past history of epilepsy. The pattern of ASM use does not correlate well with seizure onset (usually early childhood but there appears to be a second peak in adulthood). Most prescribing is long term, suggesting a reluctance to withdraw ASMs. Many PwID with a past history of epilepsy remain seizure free and should be considered for ASM withdrawal. Given the multi-dimensional challenges at the patient, clinician and resource level,^{59,60} this remains a poorly engaged topic but requires more research and coproduced engagement to reduce and prevent iatrogenic harm.

AUTHOR CONTRIBUTIONS

All authors satisfy the ICMJE guidance by substantially contributing to the design, analysis and interpretation of the work, drafting of the manuscript, final approval of the manuscript and all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work is appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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