# Title Page

**Full title of manuscript:**

Measurement of side effects of anti-epileptic drugs (AEDs) in adults with intellectual disability: A systematic review.

**Authors' names:**

Lauren Copeland[2], Andrea Meek[1], Mike Kerr[3], Michael Robling[1], Kerry Hood[1] and Rachel McNamara[1]

**Institutional Affiliation:**

[1] South East Wales Trials Unit, Centre for Trials Research, Cardiff University, Cardiff, United Kingdom

[2] Division of Population Medicine, Cardiff University, Cardiff, United Kingdom

[3] Institute of Psychological Medicine and Clinical Neuroscience, Cardiff University, Cardiff, United Kingdom.

**Contact information for corresponding author:**

Andrea Meek, South East Wales Trials Unit, Centre for Trials Research, College of Biomedical & Life Sciences, Cardiff University, 4th Floor, Neuadd Meirionnydd, Heath Park Cardiff, CF14 4YS

Tel: +44(0)29 20687619

Email: meek@cardiff.ac.uk

**Highlights**

- Out of a total of 108 measures identified, only eight were appropriate for use with people with ID.
- Screening tools are available to assess AED side effects in general adult populations; there are only two measures specifically designed for use in ID populations.
- The focus of these measures is broader than side effects and so may not pick up the full range of side effects of importance in this group.
- Side effects of AEDs are inconsistently and inadequately measured in ID populations and are overly reliant on carer report. Overall side effect burden is therefore likely to be under-reported.
- There is a clear lack of established and validated assessment scales for patients with ID and epilepsy.

**Key Words**

Intellectual Disability

Epilepsy

AED

Side-effect

PROM

## 1. Introduction

The prevalence of epilepsy in adults with an intellectual disability (ID) is up to 20 times greater than in the general population [1]. A recent survey of carers and professionals showed considerable concern over presence and impact of side effects from anti-epileptic drug (AED) treatment in people with ID (in particular drowsiness, memory problems, depression) [2] . The term *side effect* typically relates to any secondary undesirable effect of a treatment or drug. Physical, cognitive, behavioural or emotional side effects can cause significant impact on the quality of life of an individual. Monitoring side effects in adults with ID and epilepsy is challenging due to the commonly co-existing occurrence of behaviour and communication disorders [3]. The incidence of side effects is estimated to be as high as 58% in the wider population receiving treatment (i.e. adults with epilepsy without ID) [4]. Javed (2015) noted that patients with ID were less likely to report side effects than patients without ID, especially in regard to cognitive adverse events [5]. A recent Cochrane review concluded that side effects in the ID population are similar to the general population, however the authors note that this is concluded from limited studies with unreliable measures [6].

The importance of Patient Reported Outcome Measures (PROMs) in assessing health status is increasingly acknowledged, both in research and in the evaluation of routine clinical care. In a report published in 2009 [7], the Medical Research Council (MRC) suggest several key areas for future research, including addressing gaps in currently available PROMs, such as for use at end of life and in children. However, the gap in available PROMs for use with adult ID populations and their families/carers would seem to be greater still. Screening tools are available to assess AED side effects in the general adult population, and research suggests that active monitoring is sufficient to change management and improve quality of life (QoL) [8]. It is not known however whether such tools can be used to identify side effects in adults with ID, or whether included items are important and relevant to patients and carers. The importance of developing PROMs that are reliable, valid and sensitive to change within the context of clinical trials has also been highlighted [9] and

specification, selection and measurement of appropriate outcomes is central to all stages of the MRC guidance on complex intervention development [10]. However, a Cochrane review concluded that the measurement of side effects in this population was hampered by reliability of available measures [11]. In addition those with ID (and individuals with low literacy levels) are often excluded from the PROMs development process [9]. Therefore measures may not be accessible or acceptable to this population and are likely therefore to produce unreliable data if poorly completed. This group is therefore at risk of exclusion from routine patient monitoring and quality improvement schemes thus increasing potential health inequalities [9].

The aim of this focused review is to identify literature on the measurement and impact of AED side effects in adult ID populations. Specifically, we wanted to determine whether side effects and their impact were being measured, and if so by what methods including whether self- or observer-reported and the nature of domains assessed. However, given that development of measures specific to this population has received little attention to date, we will also seek to identify measures of AED side effects in the wider adult epilepsy population that may be suitable for adaptation in ID populations. Results relating to identified side effect domains (e.g. adaptive functioning, cognitive symptoms) will be summarised according to population, medication type and AED/QoL measures where the data allow. This review forms part of a wider study which aims to develop a psychometrically sound measure of AED side effects that professionals can use in consultations with patients and carers to identify the important side effects of anti-epileptic drug (AED) treatment in adults with intellectual disability.

## 2. Methods

### 2.1 Study eligibility criteria

Selected studies met the following inclusion criteria:

- Adults with epilepsy (and an identified subset with ID)
- Participants were taking at least one AED as part of their treatment regime
- Side effect outcome measure included
- Qualitative or quantitative data
- Articles published in English only.

Side effect outcome measures as stated in the methods section of the paper included, but were not limited to the following domains: seizure severity/frequency; psychiatric symptoms; social function; cognitive functioning; challenging behaviour; mood; quality of life; physical symptoms.

Studies were excluded if the seizure disorder occurred as a side effect of medical treatment or was not specified as epilepsy. Papers were excluded where no outcome data had been published. Papers reported from on-going studies which may be relevant (e.g. some feasibility / qualitative investigation of side effects which then informed outcome assessment) were included. For the full list of search terms see Appendix A.

**2.2 Information Sources**

Research articles were identified from MEDLINE In-Process, MEDLINE, EMBASE, SCOPUS and Web of Knowledge. We did not stipulate a date restriction. The search resulted in findings from; MEDLINE In-Process; 1946, MEDLINE; 1946, EMBASE; 1947, SCOPUS; 1945 and Web of Knowledge; 1950 all finishing in May 2015. We did not however search contact authors for any unpublished data.

### 2.3 Search strategy

Appropriate keywords were used e.g: epilepsy, anti-epileptic drug, anticonvulsants, outcome measures/ment, scales, side effects, tolerability, seizure severity and frequency, psychiatric, cognition challenging behaviour, mood and quality of life (for details of the full search strategy see Appendix A). Each search term was classified under one of 4 categories: participants, medication, measures and side effect domains, which were combined (requiring all four domains to be included) in the database searches.

### 2.4 Data collection

Identified papers (n=462) were assessed independently by two researchers and checked for eligibility of abstract and title according to the inclusion and exclusion criteria (see Appendix A). Studies that met inclusion criteria (n=153) were obtained in full text and again checked for eligibility against the same criteria by one researcher. 40% were double checked independently for eligibility by a second researcher. Any disagreements identified were reviewed by both researchers and discussed to resolve differences. 95 eligible papers were included in the review.

### 2.5 Data extraction

A data extraction spreadsheet was created based on the research question. The data extraction fields included recruitment data, epilepsy and ID diagnosis, outcome measure and who completed the measure. The data extraction sheet was piloted and minor amendments made prior to being finalised.

### 2.6 Data synthesis

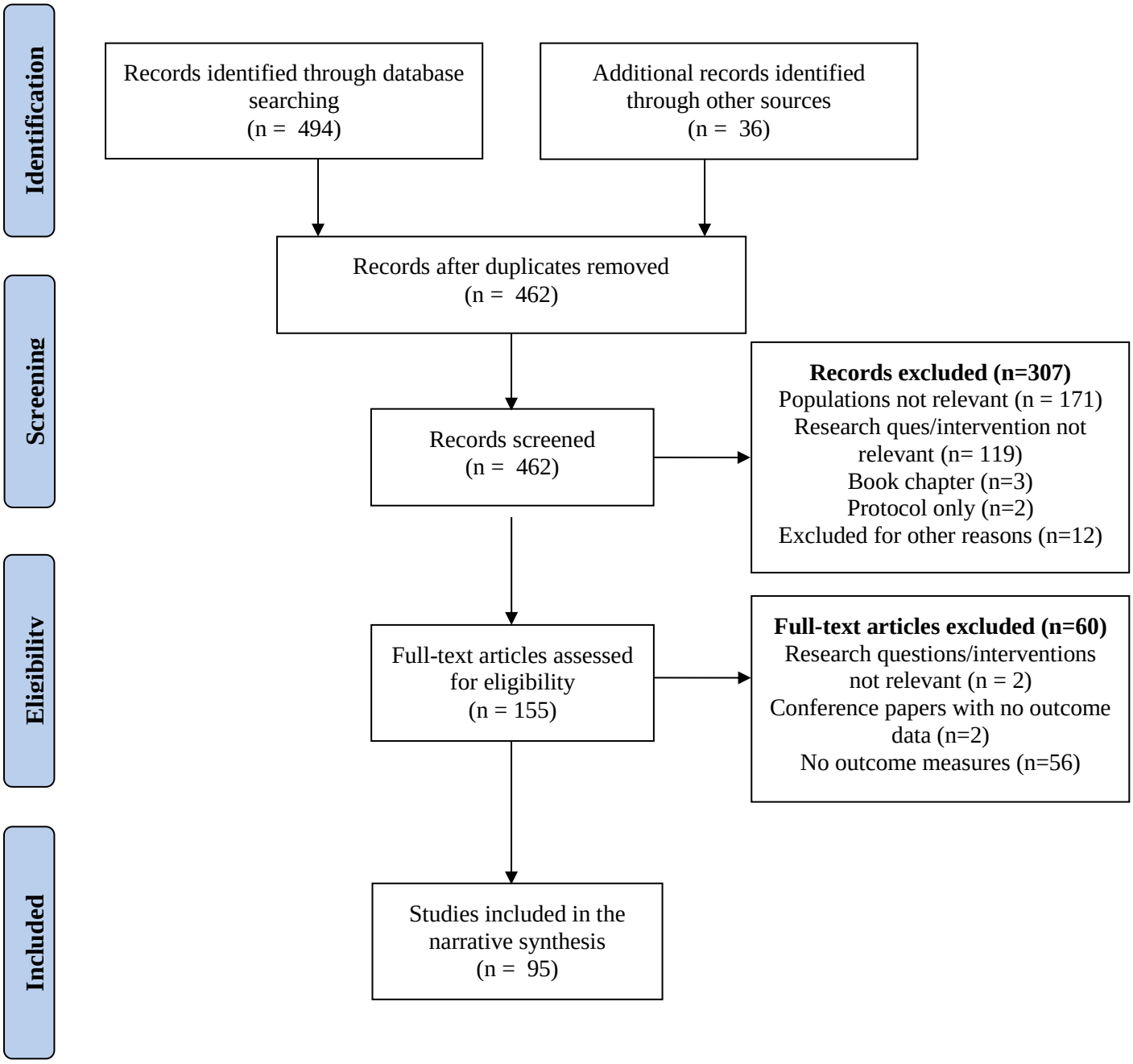
Each paper was summarised descriptively in terms of AED type, side effect domain, AED/QoL measures and who rated the measure (i.e. patient, carer/professional, proxy). Due to the nature of the review aim, it was not possible to carry out a meta-analysis and a narrative synthesis was performed instead to summarize the outcome measures. Narrative synthesis is a systematic review and synthesis

of multiple studies that is summarized in text format. The review had originally aimed to include a meta-analysis looking at associations between side effects and other important outcomes e.g. psychological well-being and challenging behaviour however no such data were reported.

## 3. Results

The initial search via electronic databases yielded 494 records and an additional 36 records were identified through hand searching. Subsequent removal of duplicates resulted in 462 papers remaining **(see Figure 1)**. Following independent review by two researchers of the abstracts according to the inclusion and exclusion criteria 153 studies were included for full paper review. From this selection 95 studies were identified as suitable for inclusion for the purposes of review.

**Figure 1: Diagram of review studies**



### 3.1 Summary of studies by side effect domain and measure in general and ID adult epilepsy populations

Table 1 presents a summary of studies by side effect domain and measure. The side effects measured by the studies range from adverse events, behavioural and cognitive changes, through to sexual functioning and quality of life. There are 108 measures used across all the studies. Eleven of these measures were used in the ID studies. Of the 108 measures, eight are designed for use with people with ID. The majority (51) of the measures for the general adult population were to be rated by the participant. This is in contrast to the measures used in the ID studies which were carer-rated.

**Table 1: Summary of studies by side effect domain and measure**

| **Table 1: Summary of studies by side effect domain and measure** | | | | |
|---|---|---|---|---|
| **Side Effect Domain** | **Measure** | **ID specific Yes/ No** | **Rater according to study** | **Paper Reference** |
| Adaptive functioning | Adaptive Behaviour Scale - Revised (ABS-R) | Yes | Carer | Kerr et al (2005) [12] |
| Adverse Effects | Liverpool Adverse Events Profile (LAEP) | No | Self | Martins et al (2011) [13], Zou et al (2014) [14], Hakami et al (2012) [15] |
| | Scale for the Evaluation and | Yes | Carer | Matson et al (2005) [16] |

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|---|---|---|---|---|
| | Identification of Seizures, Epilepsy, and Anticonvulsant Side Effects-B (SEIZES B) | | | |
| | Adverse Event Profile (AEP) | No | Self | Maschio et al (2012) [17], Villagran et al (2015) [18] |
| | WHO Toxicity Grading Scale for Determining the Severity of Adverse Events | No | Unclear | Wu et al (2009) [19] |
| | Veterans Administration Cooperative study (Neurological and Systemic Adverse Event Rating Scales [N&SAERS]) | No | Researcher | Chmielewska et al (2001) [20], Chmielewska et al (2013) [21] |
| Anxiety | Zung Anxiety Scale (ZUNG- | No | Researcher | Ketter et al (1996) [22] |

| | | | | |
|---|---|---|---|---|
| | ANX) | | | |
| | Hospital Anxiety and Depression Scale (HADS) | No | Self | Gillham et al (2000) [23], Hardan et al (1999) [24], Martins et al (2011) [13], Mosaku et al (2006) [25], Nabukenya et al (2014) [26], Pataraia et al (2013) [27], Smith et al (1993) [28], Tang et al (2012) [29], Tsounis et al (2011) [30] |
| | Hamilton Anxiety Scale (HARS) | No | Self | Martinovic et al (2004) [31], Mazza et al (2007) [32], Mazza et al (2008) [33], Tang et al (2012) [29] |
| | Beck Anxiety Inventory (BAI) | No | Self | Kim et al (2012) [34] |
| Behaviour | Matson Evaluation of Social Skills in Individuals with Severe Retardation (MESSIER) | Yes | Carer | Martin et al (2009) [35] |

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|---|---|---|---|---|
| | Aberrant Behavior Checklist (ABC)- Total | Yes | Carer | McKee et al (2003) [36], Mckee et al (2006) [37], Martin et al (2009) [35], Sunder et al (2006) [38], Kerr et al (2005) [12] |
| Behavioural adjustment | Minnesota Multiphasic Personality Inventory-2 (MMPI-2) | No | Unclear | Hessen et al (2008) [39] |
| Behavioural disturbance | Whelan and Speake Rating Scale | Unclear | Unclear | Crawford et al (2001) [40] |
| Challenging Behaviour | Key Carer-rated Visual Analogue Scales | Yes | Carer | Crawford et al (2001) [40] |
| Cognitive | Mini Mental state examination (MME) | No | Self | Wu et al (2009) [19] |
| | Dementia rating scale | No | Self | Martin et al (2005) [41] |
| | Digit Span Forward | No | Researcher | Kalviainen et al (1995) [42] |

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|---|---|---|---|---|
| | Korean-California verbal learning test (K-CVLT), | No | Unclear | Kim, D. et al (2012) [34] |
| | Stroop Color–Word Interference | No | Self | Lee et al (2011) [43], Xu et al (2007) [44] |
| | EpiTrack | No | Unclear | Lutz et al (2005) [45] |
| | Wechsler memory scale | No | Self | Martin et al (2005) [41] |
| | Montreal Cognitive Assessment (MoCA) | No | Unclear | Nakhutina et al (2015) [46] |
| | Corsi Block Span | No | Self | Kalviainen et al (1995) [42] |
| | Korean-Boston naming test (K-BNT) | No | Unclear | Kim, D. et al (2012) [34] |
| | Controlled oral word association test | No | Self | Martin et al (2005) [35] |
| | Alternating S Task | No | Researcher | Kalviainen et al (1995) [42] |
| | A-B | No | Unclear | Nakhutina et al (2015) [46] |

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| | Neurotoxicity Scale. | | | |
| | The A—B Neuropsychological Assessment Schedule | No | Unclear | Satischandra et al (2014) [47] |
| | Rivermead Behavioural Memory Test (RBMT) | No | Researcher | Brandt et al (2015) [48] |
| Cognitive/ IQ | Wechsler Adult Intelligence Scale | No | Self | Kalviainen et al (1995) [42], Kim et al (2012) [34], Lee et al (2011) [43], Lutz et al (2005) [45], Sun et al (2008) [49], Sunmonu et al (2008) [50], Xu et al (2007) [44], Brandt et al (2015) [48] |
| Depression | Beck Depression Inventory (BDI) | No | Self | Fakhoury et al (2008) [51], Rani et al (2014) [52], Villagran,et al (2015) [18], Mazza et al (2007) [32], Cho et al (2011) [53], Martinovic et al (2004) [31] |

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|---|---|---|---|---|
| | Hamilton Depression Scale (HAM-D) | No | Self | Martinovic et al (2004) [31], Mazza et al (2007) [32], Mazza et al (2008) [33] |
| | Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) | No | Self | Rathore et al (2013) [54], Fakhoury et al (2008) [51], Ettinger et al (2014) [55], Williams et al (2011) [56] |
| | Global assessment of severity of epilepsy (GASE) scale | No | Unclear | Wiebe et al (2014) [57] |
| | Cornell Dysthymia Rating Scale-Self-Report (CDRS) | No | Self | Hardan et al (1999) [58], Mazza et al (2007) [32], Martinovic et al (2004) [31] |
| | Patient Health Questionnaire (PHQ-9) | No | Unclear | Rathore et al (2013) [54] |
| | Center for Epidemiologic | No | Self | Ettinger et al (2014) [55], Mei (2006) [59] |

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| | Studies Depression Scale (CES-D) | | | |
| | Geriatric Depression scale | No | Self | Martin et al (2005) [41] |
| Disability | Global Assessment of Epilepsy-Related Disability (GAERD) | No | Unclear | Sajobi et al (2014) [60] |
| Functionality | Crichton Royal Behavioural Rating Scale | No | Unclear | Crawford et al (2001) [40] |
| | Habilitative Improvement Scale | No | Carer | McKee et al (2003) [36], McKee et al (2006) [37], Sunder et al (2006) [38] |
| Health | General Health Questionnaire (GHQ-28) | No | Self | Gillham et al (1993) [61] |
| | Patient Health Questionnaire-9 (PHQ-9) | No | Self | Tesar et al (2011) [62] |

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| | Mental Health Inventory(MHI -5) | No | Unclear | Wagner et al (1995) [63] |
| Quality of life | SEALS Side Effects and Life Satisfaction inventory | No | Self | Gillham et al (1996) [4], Gillham et al (2000) [23], Leach et al (1997) [64] |
| | Profile of Mood States (POMS) | No | Self | Ettinger et al (2007) [65], Fakhoury et al (2008) [51], Gillham et al (2000) [23] (Validation paper), Nakhutina et al (2015) [46], Salinsky et al (2005) [66], Smith et al (1993) [67] (Outcomes paper), Smith et al (1993) [28] (Seizure paper) |
| | Quality of Life Assessment Schedule (QOLAS) | No | Unclear | Kaiser et al (2002) [68] |
| | Epilepsy Outcome Scale (EOS) | Yes | Researcher | Kerr et al (2005) [12] |

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|---|---|---|---|---|
| | Epilepsy and Learning Disabilities Quality of Life (ELDQoL) | Yes | Researcher | Kerr et al (2005) [12] |
| | EORTC-QLQ-C30 | No | Unclear | Maschio et al (2012) [17] |
| | 15D HRQoL instrument | No | Self | Stavem et al (1998) [69] |
| | Medical Outcomes Study - Cognitive Functioning (MOS-COG) | No | Self | Gillham et al (2000) [23] (Validation paper), |
| | Nottingham Health Profile (NHP) | No | Self | Smith et al (1993) [67] (Outcomes paper), Smith et al (1993) [28] (Seizure paper) |
| | TTO (Time Trade Off method) | No | Self | Stavem et al (1998) [69] |
| | Visual Analogue Scale (VAS) | No | Unclear | Chmielewska et al (2001) [20], Jozwiak et al (2000) [70], |

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|---|---|---|---|---|
| | | | | Villagran et al (2015) [18] |
| | Quality of Life in Epilepsy 89 (QOLIE-89) | No | Self | Engel et al (2012) [71], Hakami et al (2012) [15] |
| | Quality of Life in Epilepsy-Problems (QOLIE-31-P) | No | Self | De Backer et al (2012) [72], Dunlap et al (2014) [73], Anders et al (2015) [74], Heo et al (2007) [75] |
| | Quality of Life in Epilepsy (QOLIE-31) | No | Self | Marson et al (2007) [76], Maschio et al (2012) [17], Mosaku et al (2006) [25], Nabukenya et al (2014) [26], Fritz et al (2005) [77], Heo et al (2012) [78], Zou et al (2014) [14] |
| | Quality of Life in Epilepsy (QOLIE-10) | No | Self | Satischandra et al (2014) [47], Semah et al (2014) [79] |
| | Quality of Well-Being Self-Administered | No | Self | Gao et al (2013) [80] |

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|---|---|---|---|---|
| | Scale (QWB-SA) | | | |
| | WHO Quality of Life-Brief version | No | Unclear | Shaw, D. et al (2015) [81] |
| | EuroQol instrument | No | Self | Stavem et al (1998) [69], Selai et al (1999) [82] |
| | Quality of Life Questionnaire (QOL-Q) | Yes | Self | Wang, T. G. et al(2008) [83] |
| | Short-form 36 | No | Unclear | Baker et al (2002) [84], Smith et al (1993) [67], Wagner et al (1995) [63], Williams et al (2011) [56] |
| | Quality of Life in Epilepsy 48 (QOLIE AD-48) | No | Self | Engel et al (2012) [71] |
| | 30-item General Health Questionnaire (GHQ-30) | No | Unclear | Mosaku et al (2006) [25] |
| | Medical Outcomes Survey Short | No | Unclear | Semah et al (2014) [79] |

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| | Form 12 (SF12) | | | |
| | Social Problems Questionnaire | No | Self | Smith et al (1993) [67] |
| | NEWQOL (Newly Diagnosed Epilepsy Quality of Life) | No | Self | Marson et al (2007) [76] |
| | Modified Mini Mental State Examination (mMMSE) | No | Unclear | Mosaku et al (2006) [25] |
| | Impact of Epilepsy (IoE) Scale | No | Self | Marson et al (2007) [76], Satischandra et al (2014) [47] |
| Impulsiveness | Barratt Impulsiveness Scale-11 (BIS-11) | No | Unclear | Helmstaedter et al (2008) [85] |
| Medication response | Side Effect of Anti-Epileptic Drugs Ques. | No | Self | Uijl et al (2009) [86] |

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|---|---|---|---|---|
| | (SIDAED) | | | |
| Mental and psychological health | Columbia-Classification Algorithm of Suicide Assessment (C-CASA) | No | Unclear | Biton et al (2015) [87] |
| | Columbia-Suicide Severity Rating Scale (C-SSRS) | No | Self | Biton et al (2015) [87], Rani et al (2014) [52] |
| | Bunney-Hamburg Rating Scale | No | Researcher | Ketter et al (1996) [22] |
| Mood | Befindlichkeits-Skala (BFS) | No | Unclear | Fritz et al (2005) [77] |
| | Cornell Dysthymia Rating Scale—Self-Report (CDRS) | No | Unclear | Hardan et al (1999) [58], Mazza et al (2007 [32], Ettinger et al (2007) [65], Martinovic et al (2004) [31] |
| | Profile of Mood States (POMS) | No | Unclear | Nakhutina et al (2015) [46] Salinsky et al (2005) [66], Ettinger et al (2007) [65], |

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| | | | | Gillham et al (2000) [23], Fakhoury et al (2008) [51], Smith et al (1993) [67] |
| | Amsterdamse Stemmingslyst (ASL) | No | Self | Aldenkamp et al (1994) [88] |
| | Montgomery and Asberg Depression Rating Scale (MADRS) | No | Researcher | Mazza et al (2008) [33] |
| | Portland Neurotoxicity Scale (PNS) | No | Unclear | Salinsky et al (2005) [66] |
| | Delighted-Terrible Scale | No | Self | Satischandra et al (2014) [47] |
| | Zung Self Rating Scale for Depression (Z-SDS) | No | Self | Mazza et al (2008) [33] |
| Personality | Fragebogens zur Persönlichkeit bei zerebralen Erkrankungen | No | Unclear | Helmstaedter et al (2008) [85] |

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|---|---|---|---|---|
| | (FPZ) | | | |
| Psychomotor performance | Digit-Symbol Substitution Test [DSST] | No | Unclear | Altman et al (2013) [89] |
| Psychopathological function | Symptom Checklist 90—Revised (SCL-90-R) questionnaire | No | Self | Wu et al (2009) [19] |
| Sedation | Stanford Sleepiness scale | No | Unclear | Altman et al (2013) [89], Salinsky et al (1996) [90], Shah et al (2010) [91] |
| | Epworth Sleepiness scale (ESS) | No | Unclear | Bonanni et al (2004) [92], Cho et al (2011) [53], Foldvary et al (2001) [93], Shah et al (2010) [91] |
| | Observer's Assessment of Alertness/Sedation Scale | No | Researcher | Altman, et al (2013) [89] |
| | Sedation score | No | Self | Gillham et al (1993) [61] |
| Seizure severity | Clinical Global Impression of Change | No | Self | Anders et al (2015) [74], Tsounis et al (2011) [30] |
| | Liverpool | No | Researcher | Baker et al (2002) [84], |

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|---|---|---|---|---|
| | Seizure Severity scale (LSSS) | | | Tesar et al (2011) [62] |
| | National Hospital Seizure Severity Scale (NHS3) | No | Clinician | Cho et al (2011) [53], Kaiser et al (2002) [68], Peng et al (2014) [94], Zou et al (2014) [14] |
| | Seizure Severity Scale | No | Unclear | Smith et al (1993) [67] |
| Sexual function | Changes in Sexual Function Questionnaire (CSFQ) | No | Self/ Researcher | Gil-Nagel et al (2006) [95] |
| | Arizona Sexual Experience scale (ASEX) | No | Unclear | Luef (2008) [96], Shah et al (2010) [91] |
| | International index of Erectile Function-15 | No | Unclear | Shaw, D. et al (2015) [81] |
| | Sexual Self efficacy scale for erectile | No | Unclear | Shaw, D. et al (2015) [81] |

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|---|---|---|---|---|
| | functioning | | | |
| Sleep | Medical Outcomes Study (MOS) Sleep Scale | No | Self | de Haas et al (2007) [97] |
| | Pittsburg Sleep Quality Index (PSQI) | No | Unclear | Peng et al (2014) [94], Cho et al (2011) [53] |
| | Groningen Sleep Questionnaire (GSQ) | No | Self | de Haas et al (2007) [97] |
| Symptom severity | 25-item Seizure Severity Questionnaire (SSQ) | No | Self | Ettinger et al (2014) [55] |
| | Global Evaluation Scale (GES) | No | Researcher | Heo et al (2007) [75], Heo et al (2012) [78] |
| Well Being | SEALS Side Effects and Life Satisfaction inventory | No | Self | Gillham et al (1996) [4], Gillham et al (2000) [23], Gillham et al (2000) [98], Leach et al (1997) [64], Marson et al (2007) [76] |

### 3.2 Summary of studies with a focus on Intellectual Disability

Within the 95 papers identified as suitable for inclusion, the reviewers found eight studies that looked at adults with epilepsy and ID, who were taking an AED and measured side effects using an outcome measure. These studies have been grouped by side effect domain and AED type. Five of the studies [[35], [37],[38], [85]] examined only behavioural domains. One paper [40] looked at behaviour as well as functionality and one paper examined cognitive adverse events [48]. The final paper [12] examined both functionality and quality of life. **Table 2** summarizes studies identified which have a focus on intellectual disability.

**Table 2: Summary of studies with a focus on Intellectual Disability**

| **Table 2: Summary of studies with a focus on ID** | | | | | |
|---|---|---|---|---|---|
| **Side effect domain** | **Paper** | **Participants (number, epilepsy diagnosis and ID diagnosis)** | **Type of AED** | **Measure** | **Results** |
| Behavioural | Helmstaedter et al. (2008) [85] | •288 patients and 43 patients as a control group.<br>•The type of epilepsy was not specified.<br>•14 | 288 patients on Levetiracetam (LEV) and 43 patients on other AEDs acting as a control | •Fragebogens zur Persönlichkeit bei zerebralen Erkrankungen<br>•Barratt Impulsiveness Scale-11: BIS-11 | •Negative side effects were reported more often in patients with ID than in general adult population patients.<br>•Behavioral changes across the sample while taking LEV |

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| | | participants were described as being 'mentally retarded' with 5% being in the LEV group and 14% in the control group | group | | (12% very negative, 25% negative, 16% positive, and 6% very positive) |
| | Martin et al. (2009) [35] | •21 patients age 4 years plus.<br>•Any type of epilepsy or seizure.<br>•A moderate to severe ID (ICD-10 classification : F71, 38%; F72, 52%). | Topiramate | •Matson Evaluation of Social Skills for Individuals with Severe Retardation (MESSIER).<br>•Aberrant Behavior Checklist (ABC). | •The ABC and MESSIER tests indicated small improvements in the majority of behavioral aspects. |

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| | McKee et al. (2003) [36] | •Patients aged at least 12 years of age.<br><br>• Epilepsy with seizures classifiable by the International Classificatio n of Seizures<br><br>•An intellectual disability based on Diagnostic and Statistical Manual IV (DSM-IV) criteria. More than two-thirds were | Lamotrigine | •Percentage of patients with reductions in seizure frequency.<br><br>•Aberrant Behavior Checklist<br><br>•Habilitative Improvement Scale. Adverse events | •Majority improvements in seizure frequency, duration and intensity.<br><br>•No improvement or change in adverse events.<br><br>•No change found relative to baseline for most patients with regards to intellectual and motor functioning.<br><br>•Mean ABC scores for lethargy and stereotopy showed significant improvement,<br><br>•Mean Habilitative Improvement Scale |

| | | | | | |
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| | | severely or profoundly 'mentally retarded'. | | | scores showed significant improvement.<br><br>•Adverse events were reported in at least 5% of patients and included somnolence, dizziness, ataxia and emotional change. |
| | McKee et al. (2006) [37] | •Patients aged 12 to 20 years.<br><br>•Refractory epilepsy.<br><br>•An intellectual disability classifiable by the DSM-IV criteria. 64% had a classification | Lamotrigine | •Aberrant Behaviour Checklist<br><br>•Habilitative Improvement Scale<br><br>•Adverse events and seizure counts were recorded by caregivers throughout the | •60% of participants noted a 50% reduction in seizure frequency, 45% reported a 75% reduction, and 25% of participants reported zero seizures.<br><br>•The mean score on the Habilitative Improvement Scale improved |

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| | | of severe or profound 'mental retardation'. | | study. | significantly from baseline.<br><br>•Improvements in all 5 subdomain areas of the Aberrant Behavior Checklist.<br><br>•80% of participants did not experience any clinically relevant change in adverse effects.<br><br>•Dizziness, somnolence, and abdominal pain were infrequently reported. Vomiting was the most common adverse event. |
| | Sunder et al. (2006) [38] | •67 participants aged at least 12 years of | Lamotrigine | •Aberrant Behavior Checklist<br><br>•Habilitative | •a reduction in seizure frequency, duration and intensity for most |

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| | | age<br><br>•A epilepsy diagnosis with seizures classifiable by the International Classificatio n of Seizures.<br><br>•Mild, moderate, severe or profound 'mental retardation' based on DSM IV criteria. | | Improvement Scale.<br><br>•Seizure counts by type of seizure were recorded by caregivers.<br><br>•Adverse events recorded by caregivers. | patients.<br><br>•81% of participants in institutional settings and 64% in community settings did not experience any change in adverse events.<br><br>•The mean Habilitative Improvement Scale scores reflected improved functioning amongst the community based participants however the mean score was significantly improved in relation to the baseline phase for both groups of participants.<br><br>•Lethargy, |

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| | | | | | stereotypy, hyperactivity and inappropriate speech ABC domain scores were found to be significantly improved for the community based group.<br><br>•No differences were found in any ABC domains for the group residing in institutional settings. |
| Behavioural and function-ality domains | Crawford et al. (2001) [40] | •Participants aged 12 years and over<br><br>•Participants were diagnosed with localisation- | Gabapentin and Lamotrigine | •Key Carer-rated Visual Analogue Scales<br><br>•Whelan and Speake Rating Scale<br><br>•Crichton Royal Behavioural Rating Scale | •The results showed no difference between groups on the Visual Analogue Scales;<br><br>•Both drugs seemed to reduce challenging behaviour as rated by Whelan and |

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| | | related epilepsy.<br><br>•An intellectual disability and met the DSM-IV criteria for 'mental retardation' on a range of levels. | | •Physician's Global Rating Scale. | Speake Rating Scale.<br><br>•Functionally improved significantly with gabapentin compared to lamotrigine as rated by the Crichton Royal Behavioural Rating Scale.<br><br>•The Physician's Global Rating Scale showed statistically significant improvements over baseline ($P < 0.01$) for challenging behaviour, seizure severity and general health for both treatment groups. |
| Function-ality and | Kerr et al. (2005) [12] | •74 participants | Topiramate | •Adaptive Behaviour Scale | •Adverse events reported were |

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| quality of life domain | | aged 12 years and older.<br><br>•A diagnosis of epilepsy<br><br>•An intellectual disability defined as an IQ of <70 (classified in accordance with the International Classification of Seizures). | | •Aberrant Behaviour Checklist<br><br>•Epilepsy Outcome Scale<br><br>•Epilepsy and Learning Disabilities Quality of Life | mainly those expected from people with epilepsy who were treated with Topiramate as add on therapy.<br><br>•Placebo-treated patients reported nervousness as a side effect whereas patients on Topiramate reported somnolence.<br><br>•No significant change in reported behaviour between the Topiramate and placebo groups.<br><br>•The quality of life measures did not indicate any significant decline in quality of life. |

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| Cognitive domain | Brandt et al (2015) [48] | 26 participants<br>•A diagnosis of epilepsy and ID<br>•An intellectual disability assessed according to ICD-10 criteria | Topiramate | •Rivermead Behavioural Memory Test<br>•Digit Span Forward and backward task / Digital symbol test (HAWIE-R)<br>•Regensburger Wortflussigkeitstest (RWT)<br>•Trail Making Test (D-KEFS) | •All tests except digit span backward, naming test and RWT (letter B) showed significant differences on and off TPM, indicating an impairment of cognitive functioning by TPM in patients with ID<br>•Attention, speed, verbal short term memory and verbal fluency were affected |

All of the above studies investigate the effectiveness of specific AED drugs on participants with epilepsy and ID. The studies report the efficacy of the AED and any side effects. Several AEDs are examined and there are a mixture of results in terms of efficacy and side effects. Some of the studies report improvements within side effect domains [[16], [17], [18], [20]] whilst other studies showed no or little improvement [ [35], [82], [85] ] .

The studies use the various measures to investigate behaviour, functionality, cognitive and quality of life domains, however, studies also recorded adverse events. One study [35] reported 57 treatment-

emergent adverse events (TEAEs) in 21 of the 29 patients from a safety cohort (72.4%) during treatment. Gastrointestinal disorders and nervousness/restlessness (4 of 29 safety set patients) and tiredness/sedation/adynamia, ear/nose/throat infections, injuries, and mental state disorders (3 patients each) were the adverse effects captured most frequently [35]. Further studies [[12], [36], [37], [38]] also reported adverse events deemed to be drug-related including somnolence, dizziness, ataxia, emotional change and vomiting. Therefore although there are a number of measures which focus on side effects it is also noted that adverse event recording is an alternative way of capturing information about side effects as opposed to using specific outcome measures.

Helmstaedter et al.(2008) [85] suggest that patients with ID reported negative side effects more often than patients with normal development. This highlights the need for a measure of AED side effects for those with ID. According to the authors of the other studies [[35], [36], [37], [38]] identified in this review, ABC, MESSIER and Habilitative Improvement Scale scores are sensitive to change. Crawford et al. (2001)[40] stated that although they found no difference between the groups in their study for challenging behaviour, functioning did improve significantly with Gabapentin compared to Lamotrigine. Both groups showed statistically significant improvements over baseline ($P < 0.01$) for challenging behaviour, seizure severity and general health. The same study also found no significant change in reported behaviour between the Topiramte and placebo groups, using a specific behaviour change measure. Concurrently the quality of life measures did not indicate any significant decline in quality of life. From these results there appear to be no significant side effects from the intervention AEDs, although this may reflect the choice of measure or proxy-assessment, rather than the absence of any negative effects.

Side effects and adverse events were assessed within each study using variable methods. For example Crawford et al (2001) [40] recorded seizure occurrences in diaries and safety and tolerability were assessed by adverse event reports, however it is not noted who completed these

diaries or reports (i.e. if they were completed by the participant or the carer). Minimal details regarding method of recording adverse events and seizure occurrence are included within the method sections of these papers. For example, Sunder et al (2006) [38] notes that adverse events and seizure occurrence were recorded by caregivers however no further details are available on the formats used to collect this data. There were no studies which included self-reported measures of seizure occurrence or adverse/side effects.

The functionality domain measures included in this review were the Adaptive Behaviour Scale (ABS-R) [99], the Habilitative Improvement Scale [100] and the Crichton Royal Behavioural Rating Scale [101]. The ABS-R and Habilitative Improvement Scale were again carer rated, in the studies reported. The Habilitative Improvement Scale and Crichton Royal Behavioural Rating Scale are recommended for carer-completion, possibly to provide a more objective assessment of functionality. With the exception of the Adaptive Behaviour Scale these measures have not been developed to measure functionality in patients with ID.

The final side effect domains noted in these studies were quality of life and cognitive adverse events. In relation to cognitive changes Brandt (2015) [48] strongly recommended that these adverse events are assessed during the course of treatment, and that the effective assessment of adverse events in people with epilepsy is essential as the occurrence of such events has an impact on a persons' quality of life, in patients who are able to follow the instructions established neuropsychological instruments may be used. Quality of Life was measured using the Epilepsy and Learning Disabilities Quality of Life (ELDQoL) [102] measure and the Epilepsy Outcome Scale [103]. Both of these measures were developed specifically for people with ID to be rated by their carer. Although it is positive these measures were developed for the ID population they do not gather the data from the ID patient themselves leading to proxy quality of life scores.

**4. Measures of side effects**

**Table 3** outlines side effect measures identified within included studies. The outcome measures identified with a focus on behaviour as a side effect domain included Key Carer-rated Visual Analogue Scales [20], Matson Evaluation of Social Skills in Individuals with Severe Retardation (MESSIER) [104], Aberrant Behavior Checklist (ABC) [105], Barratt Impulsiveness Scale-11 (BIS-11) [106], Fragebogens zur Persönlichkeit bei zerebralen Erkrankungen (FPZ) and the Whelan and Speake Rating Scale [107]. All these measures apart from the Key Carer-rated Visual Analogue Scale and the Barratt Impulsiveness Scale-11 (BIS-11), were carer-rated in the reported studies. The BIS-11, FPZ and Whelan and Speake Rating Scale were not developed for use in ID populations and therefore may not take account of the potential differences in behavioural side effects experienced in ID and general adult and elderly epilepsy populations [6].

**Table 3: Measures of side effect identified within included studies**

| **Table 3: Measures of side effect identified within included studies** | | | | | |
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| **Measure** | **Focus of Measure** | **Target responder according to study** | **Target responder according to measure** | **ID specific (Yes/No)** | **Study Reference** |
| Key Carer-rated Visual Analogue Scales [40] | Challenging behaviour | Carer | Carer | Yes* | Crawford et al. (2001) [40] |
| Fragebogens zur Persönlichkeit bei zerebralen | Personality | Carer/self | Self | No | Helmstaedter et al (2008) [85] |

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| Erkrankungen (FPZ) [108] | | | | | |
| Adaptive Behaviour Scale- Revised (ABS-R) [99] | Adaptive behaviour/ functioning | Carer | Carer | Yes | Kerr et al (2005) [12] |
| Matson Evaluation of Social Skills in Individuals with Severe Retardation (MESSIER) [104] | Behaviour | Carer | Carer | Yes | Martin et al. (2009) [35] |
| Aberrant Behavior Checklist (ABC) [105] | Behaviour | Carer | Carer | Yes | Kerr et al (2005) [12] Martin et al (2009) [35], McKee et al (2003) [36], McKee et al (2006) [37], Sunder et al (2006) [38] |
| Habilitative Improvement Scale [100] | Adaptive behaviour/ functioning | Carer | Carer | No | McKee et al (2003) [36], McKee et al (2006) [37], Sunder et al (2006) [38] |
| Barratt Impulsiveness Scale-11 (BIS-11) [106] | Impulsive-ness | Carer/self | Self | No | Helmstaedter et al (2008) [85] |
| Epilepsy Outcome Scale (EOS) [103] | Concerns about epilepsy | Carer | Carer | Yes | Kerr et al (2005) [12] |

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|---|---|---|---|---|---|
| Crichton Royal Behavioural Rating Scale [101] | Adaptive behaviour/ functioning | Carer | Carer | No | Crawford et al (2001) [40] |
| Epilepsy and Learning Disabilities Quality of Life (ELDQoL) [102] | Health related QoL | Carer | Carer | Yes | Kerr et al (2005) [12] |
| Whelan and Speake Rating Scale [107] | Behavioural disturbance | Carer | Not known** | Not known** | Crawford et al (2001) [40] |
| *scale developed specifically for study<br>** out of print | | | | | |

**5. Discussion**

We chose to undertake a review of the measurement and impact of AED side effects in general and adult intellectual disability populations, with a particular focus on results relating to identifying side effect measures of AED use (e.g. adaptive functioning, cognitive symptoms) either specifically designed for use in ID populations, or that could be adapted for this purpose. We identified 95 eligible papers, eight of which [[12], [35], [36], [37], [38], [40], [48], [85]] focused specifically on ID populations. The side effects measured by the studies range from adverse events, behavioural and cognitive, through to sexual function and quality of life. The majority of the measures for the general adult population were to be rated by the participant. This is in contrast to the measures used in the ID studies which were carer-rated. These findings replicate those of Townsend et al (2012) who undertook a systematic review of quality of life measures for people with intellectual disabilities and challenging behaviours, reporting that the number of subjective (self-reported) quality of life measures appropriate for use by people with intellectual disabilities is limited [109]. Outcome measures identified in this review can be broadly categorised within the following side effect

domains; behaviour, impulsiveness, functionality, cognitive and quality of life.

The measures identified in this review do not typically contain sufficient and appropriate content to identify changes in the overall side effects of AED's in ID populations. They are generally by-proxy measures of behavior or mood change, and as such lack face and content validity in the context of drug effects. Reliability and validity of the identified measures are not therefore reported in this paper.

The term *side effect* is defined as: "Any unwanted nontherapeutic effect caused by a drug" [110]. *Adverse events* are defined in Article 2(m) of Directive 2001/20/EC as: "Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment" [111].

In the papers identified in this review, the terms "side effect" and "adverse events" are used interchangeably throughout. Such side effects or adverse events are seldom focused on in the same way and cover a wide range of impacts, for example on adaptive or challenging behaviour or quality of life. Side effects and adverse events are generally measured in an ad hoc manner, with no standardised way of recording type or frequency of occurrence. In the majority of cases, events are carer-reported or the responder is unspecified. Given the methodology otherwise reported, particularly if diaries or standardised measures are used, it is likely that assessments are made by carers if not otherwise specified.

Studies have also included adverse events reported by participants to the clinician or researcher. Furthermore, these adverse events are not explicitly addressed by the outcome measures used by the included studies within this review. As the treatment-emergent adverse events referred to above were reported voluntarily by participants, these may represent side effects that they were particularly

concerned about, were severe or that occurred most frequently.

Thompson (2013) [2] undertook a qualitative study of carer and professional views on the management of people with intellectual disability and epilepsy and found that respondents noted a number of side effects, but that the impact of these side effects was not well understood by clinicians, who in some cases demonstrated a lack of empathy with patients and families. One family member noted that including the patient in discussions helps:

*"I sometimes feel that a percentage of people taking AEDs would be, on the whole, better off without them. Side-effects are often passed off as being unimportant and the recommendation generally is to continue increasing a drug. Listening to the patient helps"* [2].

Kerr (2009) states that it is important to recognise that the majority of patients in this population are unable to self-report side effects and as such there is a tendency for only the more overt side effects (such as vomiting or weight gain) to come to the attention of the clinician [3]. Our findings suggest that side effects of AEDs are inconsistently and inadequately measured in ID populations, and as such are likely to be under-reported. This is consistent with a broader debate reported in the literature focusing on the absence of the patients' voice in drug trials. The adverse events that are reported during drugs trials are almost entirely clinicians' impressions of patients symptoms rather than the patients report [112]. Further to this issue a recent review [113] has found the clinician reporting of adverse events provides complementary information to patient reported outcome measures. Integration of these two measures could improve clinicians and policy makers interpretations of clinical trials. It is not known whether currently available PROMs used in the general adult population can be used to identify side effects in adults with ID, or whether the items included in existing measures are important and relevant to this group of patients and their carers. Furthermore, one of the two outcome measures identified that is designed for an ID population, is intended to be

rated by carers, and focuses on the more theoretical concept of quality of life (which in practice may be poorly defined) rather than on side effects of medication per se.

The results of the current review would seem to support the assertion that patients themselves may not be as involved in discussion as they should be, and that outcome measures developed specifically for use in adults with epilepsy and ID are either not available or not commonly used. Furthermore, clinicians and researchers alike appear to have a preference for using proxy rather than patient assessment. However, this may be due to availability of suitable measures.

There are several limitations within this review. In one study [85] only 14 out of 331 participants were reported to have had an intellectual disability. However this was taken from patient files and not from psychometric evaluations, so the real figure may have been different. Due to these low numbers the study may have used different measures more appropriate for the general population rather than the ID population. A further limitation of the review is that the grey literature was not searched.

The low numbers of studies identified relating specifically to the ID population shows there is a clear need for further research in this field. It should also be noted that although the majority of measures were not developed specifically for the ID patient population they may nevertheless be useful instruments within the clinical setting. Measures are frequently used for research/evaluation purposes and so further investigation would be helpful in identifying why such measures are not utilized in the clinical environment.

**6. Conclusion**

Measurement tools are available to assess AED side effects in the general adult population, however as demonstrated by this review there are limited outcome measures designed specifically to be used

in ID populations. Furthermore, the focus of these measures is broader than side effects alone, and as such they may not be sufficiently in-depth to pick up the full range of side effects of importance in this group.

Research suggests that active monitoring of AED side effects in the general adult population is sufficient to change management and improve quality of life (QoL) [8]. Therefore, there is a need for measures developed specifically to address the potentially different impact of these medications in patients with ID, given the high level of comorbidities such as Autistic Spectrum Disorder or mental health issues and concomitant medication use, as these are factors which these are factors which also need to be considered within the ID population when examining the side effects of AED medication.With regards to AED side effects in the ID population Kerr (2009) recommended within international consensus guidelines, that baseline cognitive and behavioural assessments should be made and then re-measured after drug changes, with validated measures preferred [3]. There is a lack of established and validated assessment scales for patients with ID and epilepsy, but the fact that this is a heterogenous population and there is a wide range of diversity in communication and cognitive deficits, mean it is challenging to develop a scale or measure that is suitable for all. Thornicroft and Tansella [114] suggest that important properties for patient based outcome measures are feasibility, appropriateness, reliability, validity, responsiveness, precision,
interpretability and, acceptability. In ID populations, several additional factors should also be considered in order for the measure to be truly patient reported such as adaptability for capacity, accessibility and length/completion time, to facilitate use in a busy clinical setting. Nevertheless there is a clear need to develop a psychometrically sound measure that allows patients with epilepsy and ID to self-report the side effects of their AED medication as far as is possible.

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**Disclosure of Conflicts of Interest**

None of the authors has any conflict of interest to disclose.

**Ethical Publication Statement**

We confirm that we have read the Journals' position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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## Appendix A: Search Strategy Evidence Synthesis SIDE-PRO

Research Question

What is the measurement and impact of Anti-Epileptic Drug (AED) side effects in general and adult ID populations?

### PICO

Participants: general adult population with epilepsy

Intervention: A measure or scale to measure AED side effects

Comparison: No comparison

Measurement: outcome measures/ scales of AED side effects, patient reported outcome measures

Outcomes: Side effects of AEDs, adverse effects, quality of life, cognitive function and challenging behaviour.

### Methods

A search strategy was developed for electronic databases on Ovid Medline using both keywords and MeSH headings. The developed search strategy is below. The named anti-epileptic drugs were chosen in consultation with medical professionals. The search strategy was modified to search the rest of the databases.

| Bibliographic Databases | Number of results |
|---|---|
| EMBASE | 96 |
| MEDLINE | 295 |
| MEDLINE IN PROCESS | 23 |
| SCOPUS | 8 |
| WEB OF KNOWLEDGE | 5 |

**MESH and keywords**

Participants

Epilepsy

Drugs

Anti Epileptic Drug

Anti epilep$

AED

Anticonvulsants

Felbamate

Gabapentin

Lamotrigine

Levetiracetam

Oxcarbazepine

Topiramate

Vigabatrin

Zonisamide

**Measures**

outcome measures/ment

scales

patient reported outcome measures

**Outcomes**

side effects

adverse effects

tolerability

Seizure severity and frequency

Seizure

Psychiatric

Social functioning

cognitive function

cognitive side effect

cognition

memory

challenging behaviour

behaviour/al

behaviour problems

mood

quality of life

To be eligible, studies would need to include:

Adults AND epilepsy (but we want to identify sub-set with LD/ID) AND medication AND side effects AND scale/outcome measure.