The effectiveness and tolerability of anti-seizure medication in alcohol withdrawal syndrome: a systematic review, meta-analysis and GRADE of the evidence

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ABSTRACT

Background and Aims  Anti-seizure medications (ASMs) have been used historically as treatment options in alcohol withdrawal syndrome (AWS). In the past 10 years, there have been no large-scale meta-analyses comparing ASMs with placebo or the current AWS treatment standard, benzodiazepines. We aimed to evaluate the efficacy and tolerability of ASMs in AWS. Methods  Systematic review and meta-analysis of randomised controlled trials (RCTs) via searching Medline, Embase and PsychINFO from database inception to March 2020 involving adults age >18 years with AWS. We included 24 RCTs reporting on a total of 2223 participants. Efficacy outcomes included the number of participants experiencing AWS related seizures or delirium, Clinical Institute Withdrawal Assessment for Alcohol–Revised (CIWA-Ar) score reduction and rescue medication requirements. Tolerability outcomes included adverse event rate and dropout because of adverse events, alongside severe and life-threatening adverse event rates. Quality was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE). Results  There was no evidence of significant improvements in any efficacy outcomes when comparing ASMs with placebo or benzodiazepines. When compared with benzodiazepines, ASMs demonstrated significantly increased odds of requiring rescue medications (OR = 3.50, 95% CI = 1.32, 9.28; P = 0.012). When comparing ASMs with placebo, there were significantly more dropouts because of adverse events (OR = 1.86, 95% CI = 1.05, 3.28; P = 0.034). Most results were of very low quality with the majority of included studies conducted before 2000. Conclusions  This systematic review and meta-analysis found no evidence to support general first line clinical use of anti-seizure medications in alcohol withdrawal syndrome treatment.

Keywords  Alcohol withdrawal, anticonvulsants, anti-epileptic drugs, anti-seizure medication, GRADE, meta-analysis.

INTRODUCTION

Sudden cessation of alcohol in individuals with dependence can produce a range of withdrawal symptoms. This cluster of symptoms is commonly termed the alcohol withdrawal syndrome (AWS) and can vary from mild to severe. Symptoms can include heightened autonomic nervous system activity, motor symptoms, psychiatric symptoms and seizures and delirium [1]. Untreated AWS can lead to significant morbidity and mortality. Before the introduction of effective pharmacological treatment the mortality rate of severe AWS was estimated at 35% [2].

Prolonged excessive alcohol consumption can cause a series of neuroadaptive changes and anti-seizure medications (ASMs) can modulate the balance of neural excitation and inhibition. As such, these medications have historically been considered to have utility in AWS treatment [3]. There has also been evidence suggesting some ASMs (e.g. topiramate) may be also helpful in reducing
craving for alcohol [4], therefore if certain ASMs were effective and tolerable in both the treatment of AWS and in relapse prevention the same pharmacotherapy could be continued without a need to switch medications following AWS treatment, as is current common practice [5]. This has the potential to lead to improved medication adherence and better treatment outcomes.

No ASMs have FDA approval for AWS prophylaxis or treatment to date, and current National Institute for Health and Care Excellence (NICE) guidelines offer inconsistent recommendations on ASM use, one recommending consideration of either benzodiazepines or carbamazepine in acute withdrawal [5], the other recommending only benzodiazepines [6]. As such there is a lack of clarity surrounding the current evidence of their effectiveness and tolerability. Additionally, several newer generation ASMs, including levetiracetam, eslicarbazepine acetate and perampanel have come onto the market in the 10 years since the last large-scale AWS meta-analysis was conducted [7], with some now routinely used in certain settings, such as emergency departments, as treatment for AWS seizures. To our knowledge, only three meta-analyses of specific ASMs in AWS treatment have been conducted since 2010: one examined the effectiveness of combining tiapride and carbamazepine [8], and two examined the effectiveness of gabapentin [9,10]. Additionally, no previous studies have used modern quality assessment methods such as Grading of Recommendations Assessment, Development and Evaluation (GRADE) [11] to assess the strength of any generated clinical recommendations. As such, an up to date, comprehensive picture of the efficacy and tolerability of ASMs in AWS is lacking in the literature.

The current evidence base on whether ASMs work better than placebo or the current AWS treatment standard, benzodiazepines, is not clear. We aimed to conduct a systematic review and meta-analysis, the objectives of which were: (i) to evaluate the effectiveness of ASMs in AWS treatment; (ii) to evaluate the tolerability of ASMs in AWS treatment; and (iii) to use GRADE methodology to assess the quality of evidence and the strength of any resultant recommendations.

METHODS

This study is reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [12]. The study did not require ethical approval.

Search strategy

We searched Medline, Embase and PsychINFO from 1 January 2009 to 14 March 2020, without language restriction. This period was chosen to include the latest studies after the most recent large-scale Cochrane systematic review and meta-analysis by Minozzi et al. [7], which included papers concerning use of ASMs in AWS until December 2009. We selected studies conducted before 2009 from this review’s included studies. The complete search strategy, including medical subject headings (MeSH), can be found as Supporting information Fig. S1 in the online supplementary material.

Study selection

Two authors (J.Y.L. and E.R.) initially assessed titles and abstracts and reviewed the full text of the remaining articles for inclusion. Any discrepancy was resolved by discussion, and where agreement could not be reached a third author (N.K.) was consulted. All relevant references were checked for additional citations.

The review protocol can be found as Supporting information Fig. S2 in the online supplementary material. We included studies where randomised controlled trials (RCTs) evaluated the effectiveness or tolerability of ASMs for the treatment of AWS. Included studies were those in which participants were diagnosed with AWS using the standardised criteria that were in general use at the time of the study (i.e. DSM III-IV or ICD-10) and where participants were adults age >18 years, irrespective of gender, nationality and inpatient or outpatient therapy. The range of ASMs included followed the definition of antiepileptics in the British National Formulary (BNF) and included brivaracetam, cannabidiol, carbamazepine, eslicarbazepine acetate, ethosuximide, fosphenytoin sodium, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, paraldehyde, perampanel, phenytoin, pregabalin, rufinamide, sodium valproate, stiripentol, tiagabine, topiramate, valproic acid, vigabatrin and zonisamide. Included comparisons in our protocol are listed in Fig. 1.

We excluded studies that used or combined the use of any other medications, which were not ASMs or benzodiazepines for AWS (e.g. studies using clomethiazole, phenobarbital, or tiapride were excluded).

Figure 1 Types of comparisons included in this review protocol (ASM = anti-seizure medication; BDZ = benzodiazepine)
Data extraction

Two authors (J.Y.L. and E.R.) independently extracted data from all eligible studies using a standardised data extraction spreadsheet, which can be found as Supporting information Table S1 in the online supplementary material. In the case of incomplete reporting of data, we searched studies’ online supplementary appendices and contacted authors as necessary. Any discrepancy was resolved by discussion and where agreement could not be reached a third author (N.K.) was consulted.

The main outcome extracted for ASM treatment effectiveness was the number of people experiencing an AWS related seizure. Additional effectiveness outcomes were the number of people experiencing AWS related delirium, the CIWA-Ar score reduction and the number of people requiring rescue medication. The main outcome for ASM tolerability was the number of people who dropped out because of adverse events (AEs). Additional tolerability outcomes included the number of AEs and the number of severe, life-threatening adverse events (SAEs).

Quality assessment

The quality of each outcome estimate was assessed using the GRADE framework. Each estimate is given a rating of high, moderate, low or very low quality based on scores in five domains; risk of bias, inconsistency, indirectness, imprecision and other considerations. Because of the randomised nature of the data the default quality score is high, which can then be downgraded according to the quality of the evidence for each estimate. Risk of bias was assessed using the Cochrane risk of bias assessment tool [13], (see Supporting information Fig. S3 in the online supplementary material). Two reviewers (J.Y.L. and E.R.) independently scored the quality of each study. Any discrepancy was resolved by discussion, and where agreement could not be reached a third author (N.K.) was consulted. A complete description of the GRADE quality scoring can be found in the GRADE Supporting information Tables S2–S8 in the online supplementary material.

Statistical analysis

Included studies that provided sufficient data for the calculation of summary statistics were pooled for meta-analysis. Binary outcomes were analysed by calculating the OR with 95% CI, and continuous outcomes were analysed by calculating the standardised mean difference (SMD) with 95% CI. Heterogeneity in primary outcome studies was assessed using the I² statistic. GRADE quality score was downgraded by one level if the I² was >50% but ≤75% and by two levels if the I² was >75%. We performed random-effects meta-analysis, and funnel plots were generated for each outcome with Egger’s test used to assess the potential for publication bias. All analyses were conducted in STATA IC version 15, with the significance level set at 0.05. The analysis was not pre-registered and the results should be considered exploratory.

Role of the funding source

This study was supported and funded by King’s College London. The funder had no role in study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. All authors had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

RESULTS

Results of the search

The search generated 671 unique results and 185 additional references were identified from citation searching leading to a total of 856 studies. We examined 214 full texts and included 24 studies [14–37]. A total of 190 studies were excluded; common reasons for exclusion included that the ASM intervention was used for relapse prevention and not as a treatment for AWS, the medication reported did not meet the review inclusion protocol, or there was no comparison group included in the study. Full reasons for each study’s exclusion can be found in Supporting information Table S9 in the online supplementary material.

Included studies

The 24 included studies reported on 27 interventions, in a total of 2223 participants. The PRISMA diagram in Fig. 2 describes the study selection. A description of all included study characteristics can be found in Table 1. Nine studies compared 9 different ASMs with placebo. Thirteen studies compared 8 different ASMs with benzodiazepines. Four studies combined ASMs with benzodiazepines in treatment comparison with benzodiazepines alone. There were no RCT comparing ASMs combined with benzodiazepines versus placebo in treating AWS. There were no RCTs on brivaracetam, cannabidiol, eslicarbazepine acetate, ethosuximide, fosphenytoin sodium, lacosamide, perampanel, rufinamide, stiripentol or tiagabine. A detailed list of judgement for risk of bias can be found as Supporting information Table S10 in the online supplementary material, and Supporting information Fig. S3 shows the risk of bias assessment for the included studies in the online supplementary material. Visual inspection of funnel plots and the results of Egger’s test found no evidence of publication bias for any outcome.
With regards effectiveness outcomes, there was insufficient evidence to support general first line clinical use of ASMs in AWS treatment. When comparing the number of people experiencing AWS seizures, eight RCTs with 558 participants demonstrated no evidence of a significant difference between ASMs and placebo with an overall OR of 0.81 (95% CI = 0.47, 1.41; \( P = 0.463; I^2 = 0.0\% \); Fig. 3). When comparing ASMs to benzodiazepines, three RCTs with 187 participants demonstrated no evidence of a significant difference with an OR of 0.76, 95% CI = 0.14, 4.05; \( P = 0.749; I^2 = 0.0\% \). Only one RCT demonstrated a significant reduction in the number of people experiencing AWS seizures, in 157 participants combined ASM (phenytoin) and chlordiazepoxide compared to chlordiazepoxide demonstrated a significantly reduced odds of 0.16 (95% CI = 0.03, 0.76; \( P = 0.021; I^2 = 0.0\% \)). There was, however, significant uncertainty around this estimate and when used alone phenytoin was not more effective than placebo in reducing the number of people experiencing AWS seizures [30–32], and additionally increased rescue medication requirements when compared to placebo [30]. All results were of very low quality according to GRADE (Table 2).

There was no evidence of a difference between any ASM versus placebo or benzodiazepine, or any ASM in combination with a benzodiazepine versus a benzodiazepine in the number of people experiencing AWS delirium. All results were of very low quality according to GRADE.

Of the included studies, eight were published in or before 1989, the year when the CIWA-Ar was developed. Therefore, for the majority it was impossible to report CIWA-Ar scores. A limited number of RCTs reported the mean and standard deviation of CIWA-Ar scores up to day 4 therefore, few contributed data to meta-analysis. There was no evidence of a difference between any ASM versus placebo or benzodiazepine in CIWA-Ar score up to day 4. All results were of very low quality according to GRADE.

There were statistically significant results that benzodiazepines worked better than ASMs in reducing rescue medication requirements in AWS. Although there was
| Study name     | Country | No. of participants | Inpatient/outpatient | Male (%) | Mean age/age range | Intervention | Comparison | Length of study | Outcomes          |
|---------------|---------|---------------------|----------------------|----------|--------------------|--------------|------------|-----------------|-------------------|
| Björkqvist 1976 | Finland | 105                | Outpatient           | 100      | 20–60 y; carbamazepine 40.5 ± 1.7; placebo 36.9 ± 1.6 | Carbamazepine 800 to >600 to >400 to >200 mg/d | Placebo 800 to >600 to >400 to >200 mg/d | 7d               | AE, dropout, dropoutAE |
| Hillbom 1989a | Finland | 138                | Inpatient            | 92.8     | 24–56 y            | Carbamazepine 1200 mg | Placebo 4d  | Seizure, delirium, dropoutAE |
| Malcolm 1989  | USA     | 86                 | Inpatient            | 100      | 18–65 y            | Carbamazepine 800 mg/d | Oxazepam 120 mg/d | 7d               | Dropout, dropoutAE |
| Stuppaeck 1992 | Austria | 60                 | Inpatient            | 81       | 18–65 y; carbamazepine 42.3 ± 10.8; oxazepam 41.1 ± 8.5 | Carbamazepine 800 to >600 mg/d | Oxazepam 120 to >90 mg/d | 7d               | Seizure, delirium, AE, dropout, dropoutAE |
| Malcolm 2002  | USA     | 136                | Outpatient           | 75       | 0–1 Previous detoxifications carbamazepine 37.7 ± 9.9; oxazepam 39.3 ± 9.2; multiple detoxifications carbamazepine 37.7 ± 7.4; oxazepam 38.0 ± 6.4 | Carbamazepine 600–800 to >200 mg/d | Lorazepam 6–8 to >2 mg/d | 12d              | Seizure, delirium |
| Kalyoncu 1996 | Turkey   | 83                 | NR                   | 100      | 18–65 y            | Carbamazepine (max.800 mg/d) | Diazepam (max. 80 mg/d) | 7d               | Delirium, AE, dropout, dropoutAE |
| Koethe 2007   | Germany  | 50                 | Inpatient            | 80       | 18–60 y; oxcarbazepine 48.0 (±6.2); placebo 44.9 (±6.2) | Oxcarbazepine 600 to >900 mg/d to taper | Placebo 6d | Seizure, delirium, SAE, AE, SAE |
| Krupitsky 2007b | Russia  | 127                | Inpatient            | 100      | 43.0 ± 9.7         | Lamotrigine 100 mg/d | Placebo; diazepam 30 mg/d | 7d               | Rescue, AE, SAE, dropoutAE |
| Richter 2010  | Germany  | 106                | Inpatient            | 81       | 18–65 y; levetiracetam 44.5; control 47 | Levetiracetam 2000 to >1500 to 1000 to >500 mg/d | Placebo +Diazepam | 6d               | AE, SAE, dropout |
| Trevisan 2008b | USA      | 57                 | Outpatient           | 100      | 47.7 ± 8.4         | Gabapentin 1200 mg/d | Placebo 4w | Seizure, rescue, AE, dropout, dropoutAE |
| Chourishi 2010 | India    | 46                 | Inpatient            | 100      | 38.37 ± 8.00; 18–60 y | Lorazepam 8 to >6 to >4 to >2 mg/d | 15d                | CIWA-Ar, AE, SAE, dropout, dropoutAE |

(Continues)
| Study name | Country    | No. of participants | Inpatient/outpatient | Male (%) | Main age/age range | Intervention | Comparison | Length of study | Outcomes |
|------------|------------|---------------------|----------------------|----------|-------------------|--------------|------------|-----------------|----------|
| Myrick 2009b | USA        | 100                 | Outpatient           | 77       | Gabapentin 38.4 ± 1.82; lorazepam 39.1 ± 1.83 | Gabapentin 1200 to >900 to >600 to >300 mg/d | Lorazepam 6 to >4 mg | 4d + follow-up to day | Seizure, CITWA-Ar, delirium, seizure, CITWA-Ar, AE, SAE, dropout, dropoutAE |
| Stock 2013 | USA        | 26                  | Outpatient           | 96.2     | Gabapentin 51.1 ± 7.7; chlordiazepoxide 55.8 ± 4.8 | Gabapentin 1200 to >900 to >600 to >300 mg/d | Chlordiazepoxide 100 to >75 to >50 to >25 mg/d | 7d       | Seizure, delirium, AE, SAE, dropout, dropoutAE |
| Fög 2012   | Germany    | 42                  | Inpatient            | 71.4     | Pregabalin 47.0 ± 7.4 (30–60); placebo 40.8 ± 8.1 (23–51) | Pregabalin 300 to >200 to >100 mg/d | Placebo | 7d       | Seizure, delirium, rescue, AE, dropout, dropoutAE |
| Martinotti 2010 | Italy     | 111                 | Outpatient           | 62.2     | NR                | Pregabalin 450 mg/d | Lorazepam 10 mg/d | 14d      | Delirium, rescue, AE, dropout, dropoutAE |
| Kaim 1972  | USA        | 202                 | Inpatient            | 100      | NR                | Pankakehy 30 mL IM; 60 mL PO 1st day; 20 mL IM; 40 mL PO 2nd day | Chlordiazepoxide | 10d      | Seizure, delirium, dropout, dropoutAE |
| Alldredge 1989 | USA       | 90                  | ED                   | 94.4     | Phenytoin 39.7 ± 9.3; placebo 40.6 ± 10.3 | Phenytoin 1000 mg intravenously over 20 min | infusion of an equivalent volume of 0.9% sodium chloride | 12 h seizure free observation period after study drug infusion | Seizure, rescue |
| Chance 1991 | USA        | 55                  | ED                   | 100      | NR                | Phenytoin 15 mg/kg max. 1000 mg | Placebo added to 250 mL of normal saline, and administered by infusion pump | 6 h       | Seizure |
| Rathlev 1994 | USA       | 147                 | ED                   | 96       | 41.9; >25 y       | Phenytoin 15 mg/kg | Normal saline at an equivalent volume by IV pump | 6 h       | Seizure |
| Rothstein 1973 | USA      | 200                 | Inpatient            | NR       | NR                | Phenytoin 400 mg/d, +chlordiazepoxide | Chlordiazepoxide | 5d       | Seizure, delirium |

(Continues)
| Study name          | Country | No. of participants | Inpatient/outpatient | Male (%) | Mean age/age range | Intervention                                      | Comparison                                   | Length of study | Outcomes                           |
|---------------------|---------|---------------------|----------------------|----------|--------------------|--------------------------------------------------|---------------------------------------------|----------------|------------------------------------|
| Sampliner 1974      | USA     | 157                 | Inpatient            | NR       | NR                 | Phenytoin 300 mg/d, + chloralazine                | Placebo; + chloralazine                       | 5d             | Seizure                            |
| Trevisan 2008a      | USA     | 57                  | Outpatient           | 100      | 47.7 ± 8.4         | Valproic acid 1500 mg/d or 1125 mg/d             | Placebo                                      | 4w             | Seizure, rescue, AE, dropout, dropoutAE |
| Hillbom 1989b       | Finland | 138                 | Inpatient            | 92.8     | 24–56 y            | Sodium valproate 1200 mg                         | Placebo                                      | 4d             | Seizure, delirium, dropoutAE       |
| Reoux 2001          | USA     | 43                  | Inpatient            | 97       | 48.4 ± 7.5; 33–63 y| Sodium valproate 1500 mg/d, + oxazepam           | Placebo; + oxazepam                           | 7d             | Rescue, dropout, dropoutAE         |
| Longo 2002          | USA     | 16                  | Inpatient            | 50       | 18–65 y; sodium valproate 45; benzodiazepine 46| Sodium valproate loading 20 mg/kg/day, fixed dose taper | Placebo; diazepam 30 mg/d                    | 5d detox + 6w follow up | Seizure, rescue, AE, SAE, dropout, dropoutAE |
| Krupitsky 2007a      | Russia  | 127                 | Inpatient            | 100      | 43.0 ± 9.7         | Topiramate 100 mg/d                              | Placebo; diazepam 30 mg/d                    | 7d             | Rescue, AE, SAE, dropoutAE         |
| Rubio 2010          | Spain   | 40                  | Inpatient 2 w + outpatient 1 w | 77.5     | 18–65 y; zonisamide 41.5 ± 8.21; diazepam 400–600 mg/d | Chloralazine or lorazepam via symptom triggered; fixed dose taper | Diazepam 30–50 mg/d                          | 3w             | Seizure, delirium, CIWA-Ar, rescue, AE, dropout, dropoutAE |

NR = not reported; ED = emergency department; AE = adverse event; SAE = severe, life-threatening adverse event; dropoutAE = dropout because of adverse event. 24 studies were included, which reported 27 comparisons; three studies reported on 2 different ASMs (Hillbom 1989a [carbamazepine], Hillbom 1989b [sodium valproate], Trevisan 2008a [valproic acid], Trevisan 2008b [gabapentin], Krupitsky 2007a [topiramate] and Krupitsky 2007b [lamotrigine]).
The number of subjects experiencing ≥1 seizure: ASM vs Placebo

| Study          | OR (95% CI) | ASM | Placebo | Weight |
|----------------|-------------|-----|---------|--------|
| Allbridge 1989 | 1.00 (0.30, 3.37) | 6/45 | 6/45 | 18.62 |
| Hillcorn 1989a | 0.75 (0.12, 4.70) | 3/43 | 5/49 | 9.68  |
| Hillcorn 1989b | 0.34 (0.03, 3.40) | 1/46 | 3/49 | 10.18 |
| Chance 1991    | 1.20 (0.32, 4.52) | 5/28 | 5/27 | 14.33 |
| Rother 1994    | 0.83 (0.32, 2.15) | 10/49 | 12/51 | 35.52 |
| Koelke 2007    | 1.09 (0.06, 18.40) | 1/24 | 1/26 | 3.20 |
| Trevian 2008a  | 0.32 (0.01, 8.26) | 0/19 | 0/19 | 5.24 |
| Trevian 2008b  | 0.32 (0.01, 8.26) | 0/19 | 0/19 | 5.24 |
| Overall (I² = 0.0%, P = 0.975) | 0.81 (0.47, 1.41) | 26/279 | 32/295 | 100.00 |

**Figure 3** Forest plots for the number of subjects experiencing ≥1 seizure: ASMs compared with placebo [Colour figure can be viewed at wileyonlinelibrary.com]

Evidence of reduced odds of requiring rescue medications when treating AWS with ASMs compared to placebo, when compared to benzodiazepines, there was an overall increased odds of requiring rescue medication (OR = 3.50, 95% CI = 1.32, 9.28; P = 0.012; I² = 0.0%). When examining individual ASMs versus benzodiazepines topiramate performed worse than diazepam, whereas lamotrigine and zonisamide were no different when compared to diazepam. All results were of low or very low quality according to GRADE.

**Tolerability of ASMs in AWS treatment**

With regards tolerability outcomes when ASMs were compared to placebo, five RCTs with 368 participants showed increased odds of people dropping out because of adverse events with ASMs (OR = 1.86, 95% CI = 1.05, 3.28; P = 0.034; I² = 65.2%; Fig. 4). This effect was largely driven by the contribution of two RCTs comparing carbamazepine versus placebo. There were no evidence of significant differences between ASMs versus benzodiazepines, or ASMs combined with benzodiazepines versus benzodiazepines. All estimates were of very low quality according to GRADE (Table 3).

There were no evidence of significant differences between ASMs versus placebo, and ASMs combined with benzodiazepines versus benzodiazepines in the number of subjects reporting any adverse event. However, when examining single ASMs carbamazepine caused more adverse effects when compared to placebo. Only one ASM, zonisamide, showed significantly fewer adverse event than diazepam. All estimates were of very low quality according to GRADE.

With regards to severe, life-threatening adverse events, only one RCT of 106 participants showed no evidence of a significant difference when it compared levetiracetam in combination with diazepam to diazepam alone, this result was of very low quality according to GRADE.

With regard to tolerability, an average of zonisamide 5.25 mg per day (notably higher than the average dose prescribed for epileptic disorders) was better tolerated than diazepam and was similarly effective on both reduction in the CIWA-Ar score and rescue medication requirements when compared with diazepam. Lamotrigine, at a dose of 100 mg per day, was similar to diazepam in rescue medication requirements and the adverse event rate.

**DISCUSSION**

**Summary of main results**

There was insufficient evidence to support general first line clinical use of ASMs in AWS treatment. In comparison with previously conducted studies, levetiracetam, pregabalin and zonisamide were for the first time included in meta-analysis. Because of the small number of participants, results were both merged to see the tendency of comparison results by class and examined individually. The effectiveness of ASMs in AWS treatment, as evaluated...
Table 2. GRADE table for the number of subjects experiencing ≥1 seizure.

| Study Description                                      | No. of studies | Design | Risk of bias | Inconsistency | Imprecision | Other considerations | Intervention | Control | Effect Odds ratio (95% CI) | Quality |
|---------------------------------------------------------|----------------|--------|--------------|---------------|-------------|----------------------|--------------|---------|---------------------------|---------|
| ASM vs placebo [15,20,23,30–32]                         | 8              | RCT    | Very serious | None           | None        | None                 | 273          | 285     | 0.81 (0.47, 1.41)         | Very low |
| ASM vs benzodiazepine [17,26,29]                         | 3              | RCT    | Very serious | None           | None        | None                 | 102          | 95      | 0.76 (0.13, 4.05)         | Very low |
| ASM (phenytoin) + benzodiazepine vs benzodiazepine [34]  | 1              | RCT    | Very serious | None           | None        | None                 | 78           | 79      | 0.75 (0.12, 4.20)         | Very low |
| Carbamazepine vs placebo [15]                           | 1              | RCT    | Very serious | None           | None        | None                 | 43           | 49      | 0.32 (0.10, 1.00)         | Very low |
| Carbamazepine vs benzodiazepine [17]                    | 1              | RCT    | Very serious | Serious        | None        | None                 | 30           | 30      | 0.16 (0.03, 0.74)         | Very low |
| Oxcarbazepine vs placebo [20]                           | 1              | RCT    | Very serious | None           | None        | None                 | 24           | 26      | 1.09 (0.06, 19.07)        | Very low |
| Gabapentin vs placebo [23]                              | 1              | RCT    | Very serious | None           | None        | None                 | 19           | 19      | 0.32 (0.01, 8.24)         | Very low |
| Gabapentin vs benzodiazepine [26]                        | 1              | RCT    | Very serious | None           | None        | None                 | 9            | 17      | 1.73 (0.05, 53.50)        | Very low |
| Paraldehyde vs benzodiazepine [29]                      | 1              | RCT    | Very serious | None           | None        | None                 | 46           | 46      | 0.83 (0.05, 14.46)        | Very low |
| Phenytoin vs placebo [30–32]                            | 1              | RCT    | Very serious | None           | None        | None                 | 17           | 12      | 0.32 (0.01, 8.24)         | Very low |
| Sodium valproate vs placebo [15,23]                     | 2              | RCT    | Very serious | None           | None        | None                 | 55           | 65      | 1.23 (0.50, 3.18)         | Very low |

Quality assessment: None, Serious, None, Very serious.
by seizure/delirium prevention and CIWA-Ar score reduction, did not reveal evidence of a significant clinical improvement compared to either placebo or benzodiazepines. Although treatment with ASMs was less likely to require rescue medication than placebo, benzodiazepines worked better than ASMs in reducing rescue medication requirement in AWS, and additionally there were higher dropout rates because of AEs when compared to placebo. There is therefore no evidence that ASMs should replace benzodiazepines as a first line AWS treatment. As assessed by GRADE, most estimates were of very low quality, largely because of risk of bias as the majority of RCTs were conducted before 2000 with limited methodological reporting.

Differences exist in our study compared to previous meta-analyses [7], although three trials [16–18] on carbamazepine were shown to potentially demonstrate efficacy in reducing overall CIWA-Ar scores in the meta-analysis by Minozzi et al. It should be noted that our chosen CIWA-Ar score outcome timepoint (up to 4 days) differs from the Minozzi review (48 hours), because this was thought to be more clinically relevant, because the majority of AWS symptoms peak within the first 4 days. Additionally, all studies used high carbamazepine dosing (600–800 mg per day), significantly higher than the BNF suggested initiation dose of 100 mg/day. We demonstrate a significantly higher adverse event rate when compared to placebo [14], exacerbated by further dose increases above 1200 mg/day [15]. Although some previously conducted systematic reviews also advocate for use of certain ASMs [38], they are reported narratively and do not use meta-analytic techniques to formulate recommendations based on pooled estimates.

**Limitations of this review**

This systematic review and meta-analysis has some major limitations. There were no RCTs on ASMs in AWS treatment published since 2015; therefore limited RCT data is available for newer ASMs. Many studies had very few participants and many were conducted several decades ago, therefore, they were published in an era where there were fewer reporting standards. There was a general paucity of information on quality issues such as random sequence generation, allocation concealment and adequate blinding of outcome assessment. Furthermore, AEs were not reported clearly in the majority of studies. Participants with severe hepatic, cardiac and pulmonary diseases were excluded in most RCTs, therefore it remains unclear how patients with more complex physical health conditions would respond to ASMs as an AWS treatment.

An important limitation to the existing evidence base is that trials comparing ASMs to placebo tended to be conducted in populations with mild AWS [23,27]. Therefore, few participants may have actually required pharmacological treatment for withdrawal symptoms, and the
Table 3  GRADE table for the number of subjects who dropped out because of adverse events.

| Quality assessment | No. of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No. of patients | Effect odds ratio (95% CI) | Quality |
|--------------------|----------------|--------|--------------|---------------|--------------|-------------|----------------------|----------------|---------------------------|---------|
| ASM vs placebo [14,15,23] | 5 RCT | Very serious | Serious | None | Serious | None | 179 | 189 | 1.86 (1.05,3.28) | Very low |
| ASM vs benzodiazepine [16,17,19,28,29] | 5 RCT | Very serious | None | None | Very Serious | None | 208 | 196 | 1.41 (0.52,3.83) | Very low |
| ASM (sodium valproate) + benzodiazepine vs benzodiazepine [35] | 1 RCT | Very serious | None | None | Very Serious | None | 21 | 22 | 1.67 (0.25,11.13) | Very low |
| Carbamazepine vs placebo [14,15] | 2 RCT | Very Serious | None | None | None | None | 95 | 102 | 5.33 (2.15,13.18) | Low |
| Carbamazepine vs benzodiazepine [16,17,19] | 3 RCT | Very Serious | None | None | Very Serious | None | 116 | 113 | 1.16 (0.37,3.59) | Very low |
| Gabapentin vs placebo [23] | 1 RCT | Very Serious | None | None | Very Serious | None | 19 | 19 | 0.3 (0.03,3.14) | Very low |
| Pregabalin vs benzodiazepine [28] | 1 RCT | Very Serious | None | None | Very Serious | None | 37 | 37 | 3.08 (0.12,78.14) | Very low |
| Paraldehyde vs benzodiazepine [29] | 1 RCT | Serious | None | None | Very Serious | None | 55 | 46 | 2.56 (0.10,64.35) | Very low |
| Sodium valproate vs placebo [14,23] | 2 RCT | Very Serious | Serious | None | Very Serious | None | 65 | 68 | 0.86 (0.35,2.12) | Very low |
requirement for rescue medication may have been so infrequent that any differences between groups would have required large numbers to ascertain [20]. As such, few patients may have been at genuine risk of developing alcohol withdrawal seizures particularly given that many studies had high dropout rates. Dropout rates in the majority of included studies were between 10% and 30%, and whereas some dropouts were because of worsening withdrawals, some were because of clinical improvement, we have attempted to capture this by examining dropout because of AEs, but note that high dropout have contributed to reduced quality of the generated estimates.

Quality of evidence

Most outcomes of this meta-analysis were rated as ‘very low’ in quality according to GRADE system, the downgrading caused mainly by high risk of bias scores because of lack of methodological reporting. There were substantially high dropout rates in most RCTs, leading to high risk of bias judgments regarding attrition bias. This is another major difference from previous studies [7], because no previous reviews have used GRADE methodology, we can report that any newly conducted trials are likely to affect almost all estimates.

Overall applicability of evidence

From this study, there are some ASMs that merit further exploration in AWS treatment. Zonisamide at 525 mg per day was better tolerated and was similarly effective at reducing both the CIW A-Ar score and rescue medication requirements compared with diazepam, and lamotrigine at 100 mg per day was similar to diazepam in reducing rescue medication requirements with similar adverse event rates. In included RCTs, zonisamide and lamotrigine were started with high dose and then tapered quickly, which may be difficult to achieve in routine clinical practice if patients are not as closely monitored as trial participants, given zonisamide and lamotrigine are usually slowly titrated because of risk of adverse drug reactions [39,40]. Therefore, lower doses of zonisamide 50 mg/day and lamotrigine 25 mg/day suggested by BNF could be tested for their effectiveness and tolerability in AWS treatment.

Whereas further RCTs are likely to change estimates, further studies of carbamazepine do not warrant further exploration given their tolerability profile. Additionally, gabapentin did not appear to reduce rescue medication requirements and pregabalin did not appear effective in CIWA-Ar score reduction. Given the growing evidence base regarding their abuse liability and toxicity [41–44], they should not be prioritised to merit urgent further study.

There were limited results on newer ASMs in AWS treatment. Levetiracetam was only combined with diazepam to be compared with diazepam alone in one RCT of 106 participants. It demonstrated no evidence of a difference in adverse event, severe, life-threatening adverse event rate or dropout rate, and therefore this combination did not appear superior in effectiveness. Levetiracetam is routinely prescribed in some United Kingdom accident and emergency departments for treatment and secondary prophylaxis of alcohol withdrawal seizures, often without benzodiazepines, perhaps because of a perceived reduced abuse liability or perhaps because of uncertainty regarding the seizure’s cause and a perception of general efficacy in seizure termination [45]. There was no evidence to support this practice.

More RCTs on participants with AWS and CIWA-Ar scores >10 are needed to have better understanding of the effectiveness and tolerability of ASMs, and we would suggest prioritisation of zonisamide, lamotrigine and levetiracetam.

CONCLUSIONS

There was insufficient evidence to support general first line clinical use of ASMs in AWS treatment. Although ASMs seemed to have limited side effects, there was limited evidence of their effectiveness compared to placebo. Included RCTs were largely conducted on small numbers of participants and the results of most outcomes did not reach statistical significance. This is the most up to date review, and the first to use GRADE to evaluate the strength of evidence. Further studies on the effectiveness and tolerability of ASMs should consider recruiting people with more severe AWS and should prioritise studies of zonisamide, lamotrigine and levetiracetam.

Author contributions

Jou-Yin Lai: Conceptualization; formal analysis; methodology; project administration. Nicola Kalk: Conceptualization; formal analysis; methodology; project administration; supervision. Emmert Roberts: Conceptualization; formal analysis; methodology; project administration; supervision.

Declaration of interests

None.

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### Supporting Information

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

**Table S1** Table for data extrac.

**Table S2** GRADE table for the number of subjects experiencing ≥1 seizure.

**Table S3** GRADE table for the number of subjects experiencing delirium.

**Table S4** GRADE table for CIWA-Ar score up to day 4.

**Table S5** GRADE table for the number of subjects requiring rescue medications.

**Table S6** GRADE table for the number of subjects who dropped out because of adverse events.

**Table S7** GRADE table for the number of subjects reporting any adverse event.

**Table S8** GRADE table for the number of subjects reporting any severe, life-threatening adverse event.

**Table S9** Full-text articles excluded, with reasons.

**Table S10** Judgement for risk of bias.

**Figure S1** Full search strategy.

**Figure S2** Review protocol.

**Figure S3** Bias assessed with the Cochrane Risk of Bias tool of the total included studies.

**Figure S4** Forest plots for the number of subjects experiencing ≥1 seizure: (a) ASM compared with placebo, (b) ASM compared with benzodiazepine, (c) ASM (phenytoin) + benzodiazepine compared with benzodiazepine.

**Figure S5** Forest plots for the number of subjects experiencing delirium: (a) ASM compared with placebo, (b) ASM (carbamazepine) compared with benzodiazepine, (c) ASM (phenytoin) + benzodiazepine compared with benzodiazepine.

**Figure S6** Forest plots for CIWA-Ar score up to day 4: (a) ASM (pregabalin) compared with placebo, (b) ASM compared with benzodiazepine.

**Figure S7** Forest plots for the number of subjects requiring rescue medication: (a) ASM compared with placebo, (b) ASM compared with benzodiazepine, (c) ASM (sodium valproate) + benzodiazepine compared with benzodiazepine, (d) topiramate compared with placebo, (e) lamotrigine compared with placebo, (f) topiramate compared with benzodiazepine.

**Figure S8** Forest plots for the number of subjects who dropped out because of adverse events: (a) ASM compared with placebo, (b) ASM compared with benzodiazepine, (c) ASM (sodium valproate) + benzodiazepine compared with benzodiazepine, (d) carbamazepine compared with placebo.

**Figure S9** Forest plots for the number of subjects reporting any adverse event: (a) ASM compared with placebo, (b) ASM compared with benzodiazepine, (c) ASM (levetiracetam) + benzodiazepine compared with benzodiazepine, (d) carbamazepine compared with placebo, (e) zonisamide compared with benzodiazepine.

**Figure S10** Forest plots for the number of subjects reporting any severe, life-threatening adverse event: ASM (levetiracetam) + benzodiazepine compared with benzodiazepine.