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Anticonvulsants in the Treatment of Behavioral and Psychological Symptoms in Dementia: A Systematic Review

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ABSTRACT

Objectives: *Behavioral and psychological symptoms of dementia (BPSD) are common and impart a significant burden to patients, caregivers, and the health system. However, there are few pharmacological options for treating BPSD. We conducted a systematic review of clinical trials examining the efficacy of anticonvulsants in BPSD.* ***Methods:*** *We searched five electronic databases through January 2023, for randomized controlled trials and systematic reviews evaluating the efficacy of non-benzodiazepine anticonvulsants for the treatment of BPSD. We used the Cochrane risk of bias tool to ascertain the risk of bias in included trials. Because statistical pooling of results using meta-analysis was not feasible, we synthesized findings using the Cochrane Synthesis Without Meta-analysis reporting guidelines.* ***Results:*** *We identified 12 studies, including randomized controlled trials (RCTs) and 1 systematic review. Five RCTs evaluating valproic acid were synthesized by a recent Cochrane review which concluded that this drug is likely ineffective for BPSD. We extracted data from 6 trials involving 248 individuals comparing non-benzodiazepine anticonvulsants to either placebo or risperidone. Four trials (n = 97 participants)*

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evaluated carbamazepine, only one of which demonstrated an improvement in the Brief Psychiatric Rating Scale measuring agitation, hostility, psychosis, and withdrawal/depression (effect size: 1.13; 95% confidence interval [CI]: 0.54−1.73) relative to placebo. Adverse effects were more common in patients receiving carbamazepine (20/27; 74%) relative to placebo (5/24; 21%). There is low quality evidence that oxcarbazepine is likely ineffective and that topiramate may be comparable to risperidone. ***Conclusion:*** *Anticonvulsants are unlikely to be effective in BPSD, although the quality of existing evidence is low.* (Am J Geriatr Psychiatry 2024; ■■:■■−■■)

Highlights

- **What is the primary question addressed by this study?**
  What is the efficacy and safety of non-benzodiazepine anticonvulsants for treating behavioral and psychological symptoms of dementia (BPSD)?
- **What is the main finding of this study?**
  Our systematic review of clinical trials found that non-benzodiazepine anticonvulsants (i.e., carbamazepine, oxcarbazepine, valproate preparations, topiramate) are unlikely to be effective in BPSD, and may be associated with a higher prevalence of adverse effects than comparator treatments. The quality of existing evidence is low.
- **What is the meaning of the finding?**
  Existing evidence does not support the use of non-benzodiazepine anticonvulsants as treatment for BPSD.

INTRODUCTION

Behavioral and psychological symptoms of dementia (BPSD) are common in people with dementia[1] and impart a substantial burden to patients, caregivers, and the healthcare system. Specifically, BPSD can result in caregiver burnout, nursing home placement,[2] and increased costs of care.[3] While non-pharmacological interventions are first line treatment of BPSD,[4] pharmacological treatment may be required in many.[5] Consequently, it is important for clinicians and decision makers to understand the risks and benefits of medications used for treating BPSD in older adults.

Antipsychotics are the most studied class of medication for the treatment of BPSD and are often used off label for this indication.[6] However, the benefits of antipsychotic treatment for symptom management in patients with BPSD appear small and must be balanced against recent studies documenting a higher risk of mortality in patients with dementia than previously estimated.[7] Antidepressants have also been studied in the treatment of BPSD with evidence both from RCTs[8] and systematic reviews.[9] However, a recent systematic review did not show strong support for antidepressants in the treatment of depressive symptoms in dementia.[10] Thus, there continues to be a need for other agents as the net benefit for commonly used medications is small.

Anticonvulsants used in the treatment of mood disorders have also been studied as potential treatments for BPSD. The means through which anticonvulsants confer benefit for BPSD are unknown and likely vary according to the individual agent used. Possible mechanisms include increasing GABAergic inhibitory neurotransmission, decreasing glutamatergic neurotransmission, inhibition of voltage-dependent sodium or calcium channels, and impacting intracellular signaling pathways.[11,12] However, evidence for the effectiveness and safety of anticonvulsants for treating BPSD is limited. Specifically, there are several descriptive reviews regarding the use of anticonvulsants for BPSD[13,14] and a Cochrane review focusing on valproic acid that was first published in

TABLE 1. Summary of Inclusion Criteria

Category	Criteria
Population(s)	Individuals with dementia and BPSD living in the community, long term care or in specialized longer stay settings.
Intervention	All anticonvulsants for BPSD including valproic acid, gabapentin, pregabalin, carbamazepine, phenytoin, topiramate, levetiracetam, zonisamide, oxcarbazepine, lamotrigine and phenobarbital. Benzodiazepines excluded.
Control	Placebo, no intervention, or other active treatments including both non-pharmacologic or pharmacologic treatments.
Outcomes	Primary outcomes: We will consider trials that use validated measures of BPSD such as 1. Neuropsychiatric Inventory 2. Cohen-Mansfield Agitation Inventory 3. Brief Psychiatric Rating Scale 4. Clinical Global Impression Scale Secondary outcomes: 1. Caregiver burden and quality of life 2. Placement in long term care facility from home 3. Serious adverse effects 4. Treatment discontinuation due to serious adverse effects
Study design timing	Randomized control trials and crossover trials. Any duration of follow-up longer than 2 weeks.

Inclusion criteria summarized from systematic review protocol (reference #19).

2004[15] and most recently updated in 2018.[16] Network meta-analyses have examined all pharmacological interventions for BPSD[17] and the comparative efficacy of non-pharmacological and pharmacological interventions.[18] However, these studies considered anticonvulsants as a single class of medications, which may obscure individual treatment benefits given their pharmacological heterogeneity. Moreover, to the best of our knowledge, there have been no systematic reviews examining the current evidence on individual anticonvulsants in the treatment of BPSD. Accordingly, we conducted a systematic review to assess the quality of evidence regarding the use of anticonvulsants for BPSD and examine the efficacy and safety of these drugs for this indication. Our specific objectives were to examine whether anticonvulsants improve patient (e.g., decrease in agitation or aggression and nursing home placement) and caregiver (e.g., burden, quality of life) outcomes in BPSD, whether these drugs differ in the risk of serious adverse events, and whether anticonvulsant treatment effects vary by type of dementia, setting in which the intervention is administered and concomitant pharmacotherapy.

METHODS

Our study protocol was registered with the international prospective register of systematic reviews (PROSPERO CRD42017079826) and is described elsewhere in detail but summarized below.[19]

Eligibility Criteria

We included randomized controlled trials of trials of non-benzodiazepine anticonvulsants (i.e., valproic acid, gabapentin, pregabalin, carbamazepine, phenytoin, topiramate, levetiracetam, zonisamide, oxcarbazepine, lamotrigine and phenobarbital) in patients with BPSD residing in the community, long term care facilities, or individuals followed at specialized geriatric assessment and psychogeriatric units (see Table 1 for eligibility criteria). We included trials comparing anticonvulsants to a variety of control conditions, including placebo, no intervention, or other pharmacologic or non-pharmacologic interventions. We excluded trials evaluating the efficacy of anticonvulsants for seizure disorders and studies conducted in acute care hospitals other than psychogeriatric units to avoid confounding by factors related to acute illness. As dementia can occur in younger adults, we did not limit the search to older adults. We included trials where the diagnosis of dementia was ascertained by clinical interview and exam using criteria specified by the Diagnostic and Statistical Manual of Mental Disorders (DSM) third, fourth or fifth editions, International Statistical Classification of Diseases and Related Health Problems tenth revision (ICD-10), or internationally recognized criteria such as the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).

Outcomes

The primary outcome was the change in behavior score measured using validated scales (see Table 1 and Supplemental Appendix for specific scales).[19] We also considered trials presenting the change in behavior as a dichotomous outcome and trials that measured outcomes using the Brief Agitation Rating scale and other less known scales, such as the RAGE scale.20 Secondary outcomes included caregiver

burden and quality of life, placement in long term care facility, rates of adverse events, and the occurrence of serious adverse effects, as defined by FDA or treatment discontinuation due to adverse effect.

Information Sources and Search Strategy

We searched five databases (Cochrane Central Register of Controlled Trials, Web of Science Update, Ovid MEDLINE, Ovid EMBASE, Ovid PsycInfo,) for all potentially relevant trials published January 2023. The search strategy was developed collaboratively with a Clinical Services Librarian at McMaster University (see Appendix 1 for MEDLINE strategy). The MEDLINE search strategy was adapted for the other databases searched. No limits were set for language though we excluded non-English language articles at a later stage.

Study Selection

Eligibility assessment at the title screening stage and at the full text stage was performed independently, in a blinded manner by two sets of reviewers (SB, JT and JH, HA). Disagreements between reviewers were resolved by consensus and discussion with a third reviewer.

Data Collection Process

Data extraction was managed through Covidence software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). Two authors (SB and SD) independently extracted trial data, and a third author (JT) reviewed the extracted data for discrepancies. We extracted data regarding study sample/patient characteristics (e.g., age, sex, comorbidities, etc.), diagnosis and types of dementia, stage or severity of dementia (defined using Mini Mental Status Exam or the Clinical Dementia Rating Scale), trial setting, support and sponsorship, starting and average dose of anticonvulsants, nature of comparison intervention (if applicable), patient follow-up, reasons for withdrawals and primary and secondary outcomes. We also extracted information about trial design features on masking, whether parallel group or cross-over, features of randomization, and sample size calculation, as well as any additional data needed to ascertain risk of bias, dropout rates and reasons why, and comments on success of masking, given the possibility of side effects unmasking patients.

Assessment of Risk of Bias in Included Trials

Two authors (SB, SD) assessed the quality of included studies using the standard Cochrane risk of bias tool[21] (version 1) in Covidence. Criteria examined for quality included sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, and selective outcome reporting and other sources of bias. Each element was rated as high, low or unclear. JT reviewed the results for discrepancies, and these were resolved by consensus.

Narrative Summary

Because some anticonvulsants were evaluated in only a single trial and there was heterogeneity in the outcome measures and quality of reporting, we could not conduct a formal meta-analysis of effect estimates. Consequently, we used the synthesis without meta-analysis (SWiM)[22] in systematic reviews guidelines to structure the synthesis.

RESULTS

Study Selection

The literature search identified 4320 citations (Fig. 1). After excluding duplicates and reviewing titles and abstracts, we assessed 89 studies for full-text eligibility. Seventy-six studies were subsequently excluded for various reasons (Fig. 1), resulting in eleven randomized controlled trials meeting our inclusion criteria. Five randomized trials of valproic acid were abstracted in a recently published high quality systematic review which was also included at the full text stage, making the total number of included studies twelve. No additional studies on valproic acid were identified in our search and we have summarized the results from the systematic review. We calculated inter-rater reliability using Covidence software. At the title screening stage, the percent agreement was 97% and disagreement calculated by Cohen's kappa was 0.51 representing moderate

FIGURE 1. PRISMA flow chart.

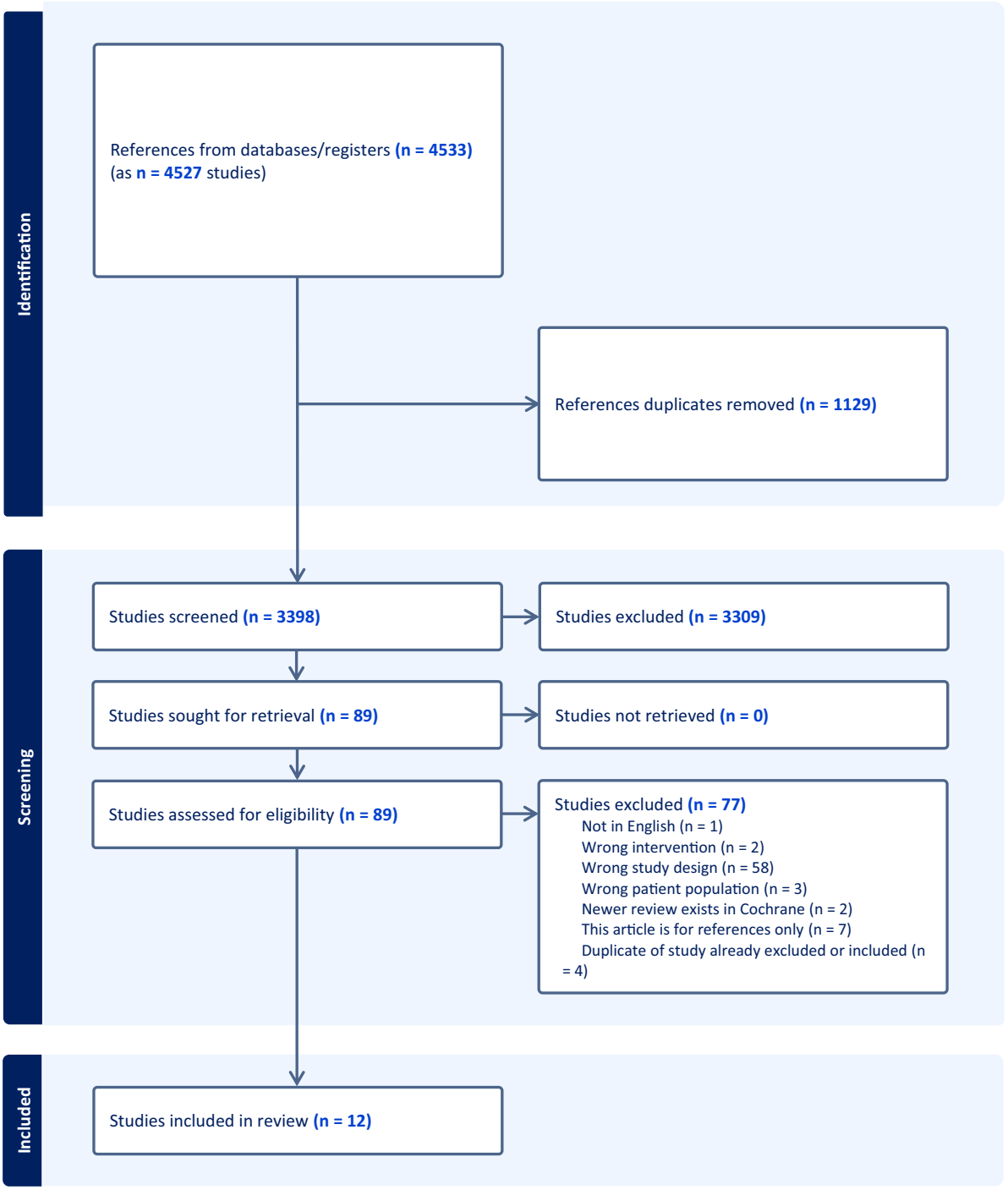
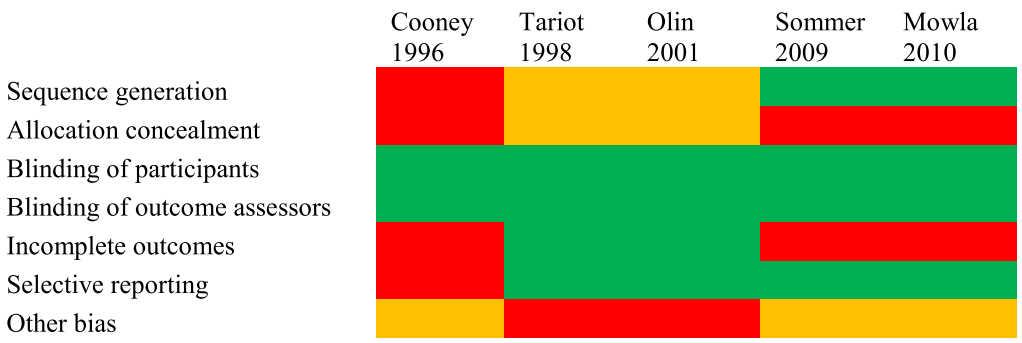


TABLE 2. Risk of Bias Within Studies



disagreement. At the full text screening stage, percent agreement was 85% and Cohen's kappa was 0.50.

Risk of Bias in Studies

The risk of bias in trials of carbamazepine, oxcarbazepine and topiramate was rated as high (Table 2). Specifically, of the five trials from which data could be extracted, only two described sequence allocation and none described allocation concealment. Although all trials provided information on blinding of participants and assessors, three trials had incomplete reporting of outcomes, and all trials had small sample sizes and durations of follow-up (i.e., 4–12 weeks) that are likely too short to ascertain the efficacy and safety of anticonvulsants for BPSD. The quality of randomized trials comparing valproic acid to placebo was assessed by two authors of a systematic review published in 2018, which found that studies were generally of moderate quality. However, only one of five studies reported on random sequence generation and only two studies reported on allocation concealment, raising the possibility of selection bias.

Study Characteristics

The trials were conducted from 1982 to 2009 across numerous countries, including the United States, Norway, Iran, United Kingdom, and Scotland (Table 3). Participants were recruited from a hospital, specialist outpatient clinics, nursing homes, and a group home. The mean age across trials ranged from 74.7 to 84 years and the baseline cognitive status as measured by the MMSE ranged from 0 in one trial of patients in a group home to 18.4 in a trial where the participants attended an outpatient clinic.

Results of Individual Studies

Carbamazepine

We identified 4 trials of carbamazepine that met the inclusion criteria.[23–26] Generally, trials were rated as low quality and high risk of bias, with small sample sizes, incomplete reporting of outcomes, and short durations of follow-up (Table 4).

In a crossover double-blind trial, six patients (average age 77.2 years) received up to 300 mg of carbamazepine twice a day or placebo for 8 weeks, with a one-week washout period between interventions.[23] The primary outcome was the RAGE scale.[20] While the trial concluded that there was a statistically significant difference in the outcome, the magnitude or clinical significance of this result could not be determined because baseline and follow-up data were not provided.

Another United States trial randomized 51 residents from multiple nursing homes to receive either carbamazepine (n = 27) or placebo (n = 24).[25] The mean age of participants was 86 years, with a mean duration of nursing home residence of 3.4 years. The average baseline BPRS and MMSE scores were 54.2 and 6.0, respectively. The modal dose of carbamazepine in the treatment group was 300 mg per day, and the primary outcome was the change in BPRS score. The a priori length of this trial is unknown as the trial was terminated early at 6 weeks based on a planned interim efficacy analysis. The BPRS score declined by 7.7 (SD = 5.7) points in the carbamazepine group and

TABLE 3. Evidence Profile of Included Trials of Oxcarbazepine, Topiramate, and Carbamazepine

Study	Setting and Location	Mean Age	Mean Baseline Cognitive Score (SD)	Duration	Intervention and n of Participants	Comparator and n of Participants	Outcome	Risk of Bias	Benefit	Harm
Sommer, 2009	Nursing homes, Norway	84 (range: 63–98),	MMSE, 5.4 (5.4), 6.2 (5.7)	12 weeks	Oxcarbazepine, n = 52	Placebo, n = 51	NPI-NH, Aggression and agitation scale; BARS	Moderate	No	Yes
Mowla, 2010	Outpatient, clinic, Iran	74.7 (3.0)	MMSE, 18.4 (3.1)	8 weeks	Topiramate, n = 21	Risperidone, n = 20	NPI, CGI	High	No	Yes
Tariot, 1998	Long term care, USA	86 (6.4)	MMSE 6.0 (7.0)	6 weeks	Carbamazepine n = 27	Placebo n = 24	BPRS, CGI	High	Yes	Yes
Olin, 2001	Pharmacology Program of the USC Alzheimer's Disease Research Center	74.7 (6.23)	MMSE 6.0 (3.6)	6 weeks	Carbamazepine n = 9	Placebo, n = 12	BPRS, CGI	High	No	Unclear
Cooney, 1996	Residential home for mentally infirm, UK	77.2 (9.2)	MMSE 0 for 5 participants, other unknown	8 weeks, Crossover trial	Carbamazepine n = 6	Placebo n = 6	RAGE scale	High	Unclear	InComplete 1 report of sedation
Chambers, 1982	Hospital, Scotland	79.8	Unknown	4 weeks, crossover with 3-week withdrawal	Carbamazepine n = 19	Placebo n = 19	Clifton Assessment Schedule	Unknown	No	Not reported

0.9 (SD = 6.3) points in the placebo group, resulting in an effect size of 1.13 (95% confidence interval [CI]: 0.54−1.73). In an analysis of caregiver burden, staff reported that the time required to attend to behavioral problems decreased in 74% of patients receiving carbamazepine (20 of 27), compared with 21% (5 of 24) of patients receiving placebo. Side effects were reported in 59% (16 of 27) and 29% (7 of 24) carbamazepine- and placebo-treated patients, respectively (p = 0.03), with two individuals reported to have clinically significant adverse effects of ataxia and tics.

A third trial enrolled 21 patients randomized to either carbamazepine (n = 9) or placebo (n = 12) following an inadequate response to antipsychotics. Patients were recruited through a pharmacology program in a specialized Alzheimer's research centre in the United States and had a mean age of 74.7 years.[27] Five patients withdrew from the trial because of lack of efficacy (n = 3), cognitive worsening (n = 1) and cerebrovascular accident (n = 1). The mean carbamazepine dose at the end of the trial was 388 mg per day. The primary outcomes were total BPRS score and Clinical Global Impression (CGI) scale . At the end of 6 weeks, there was no statistically significant difference between carbamazepine and placebo in either outcome. However, the trial was underpowered, given that total enrollment fell short of the target sample size of 61 participants determined by the investigators' sample size calculation.

A trial available only in abstract form reported on 19 female inpatients randomized to either carbamazepine or placebo in a cross-over fashion, each for four weeks.[24] Although the trial concluded that carbamazepine did not affect over-activity as measured by a ward behavior rating scale, we could not extract further data or perform a risk of bias assessment with the available information.

Other than reporting of adverse effects in two of the four studies, no other secondary outcomes were assessed and reported.

Oxcarbazepine

We identified one 8-week randomized control trial of 103 nursing home residents in Norway that comparing oxcarbazepine (up to 900 mg per day) to placebo.[27] There were no statistically significant differences in either the primary outcome of change in the NPI-NH agitation/aggression subscale and in

TABLE 4. Trials of Carbamazepine for BPSD

	Number Enrolled	Outcome	Risk of Bias	Benefit	Harm
Tariot, 1998	51	BPRS, CGI	High	Yes	Yes
Olin, 2001	21	BPRS, CGI	High	No	Unclear
Cooney, 1996	6	RAGE scale	High	Unclear	Incomplete report, sedation in 1 participant
Chambers, 1982	19	Clifton assessment schedule	Unable to assess	No	Not reported

secondary outcomes of changes in the Brief Agitation Rating Scale (BARS) and NPI-NH total burden score. The study was powered to detect a moderate difference of 1.2 on the NPI-NH agitation/aggression subscale. Of the 103 participants, a total of 63 (61.2%) experienced adverse effects. Specifically, adverse effects were reported in 75% (n = 39) and 47% (n = 24) of oxcarbazepine- and placebo-treated patients, respectively, with 50% of those randomized to oxcarbazepine experiencing a nervous system side effect (e.g., ataxia, fainting, sedation) compared to 7.8 % of those receiving placebo. The proportion of patients withdrawing from treatment was higher among patients randomized to oxcarbazepine (28.8% vs. 9.8%). Because of the large and unequal number of dropouts and the use of last observation carried forward for the imputation of missing values rather than more robust methods for handling missing data, the risk of bias was deemed high. No other secondary outcomes were reported in this study.

Topiramate

We identified one 8-week trial of 48 outpatients in Iran randomized to either topiramate (n = 21) or risperidone (n = 20).[28] There were no statistically significant differences between topiramate and risperidone in NPI1, NPI2, total NPI and the CMAI, and both groups showed a decrease in symptoms over the trial period. Four topiramate-treated patients withdrew due to side effects compared with 3 from the risperidone group (e.g., akathisia, gastrointestinal disturbances). These patients were not included in the analysis. Secondary outcomes such as caregiver burden or time to nursing home placement were not reported in this study.

Valproate preparations

We identified one good quality systematic review, completed in 2018, summarizing evidence from five clinical trials[29–33] of 450 patients who were randomized to either valproic acid or placebo (Table 5).[16] The systematic review was an update of a 2004 Cochrane review with a 2009 update. It had well defined inclusion and exclusion criteria, a comprehensive search, and assessment of risk of bias of individual studies. Two trials of 202 participants provided moderate quality evidence that valproic acid has little to no effect in reducing the total BPRS score (mean difference [MD] 0.23; 95% CI: -2.14 to 2.59) or BPRS agitation score (MD -0.67, 95% CI: -1.49 to 0.15).

In terms of adverse effects, the systematic review authors undertook a meta-analysis of three studies (n = 381 participants) showing a higher rate of adverse effects among valproate-treated patients relative to controls (odds ratio [OR] 2.02, 95% CI: 1.30 −3.14). Similarly, pooled analysis of two trials involving 228 participants found that valproate-treated patients were more likely to experience serious adverse effects (OR 4.77, 95% CI: 1.00−22.74). However, authors rated data regarding adverse effects to be of low quality and there was a high risk of heterogeneity for this analysis (I^2 = 68%). No study reported on caregiver burden or other patient and caregiver outcomes. Furthermore, no study compared divalproex preparations directly with other pharmacological or non-pharmacological interventions.

Other anticonvulsants

We did not find any trials evaluating gabapentin, pregabalin, phenytoin, levetiracetam, zonisamide, lamotrigine, or phenobarbital as treatments of BPSD that met our eligibility criteria. Although there are case studies and series describing the use of pregabalin and gabapentin for BPSD,[34] no randomized trials of these agents were available as of the time of this review.

Synthesis of Results

Overall, there is low quality evidence evaluating the use of anticonvulsants in older adults with BPSD.

TABLE 5. Evidence Profile of Trials of Valproic Acid Summarized in the Systematic Review

Study	Setting and Location	Mean Age	Mean Baseline Cognitive Score (SD)	Duration	Intervention (n)	Comparator (n)	Outcome	Risk of Bias
Porsteinsson, 2001	Long term care homes, USA	85.0 (7.1)	MMSE, Placebo: 6.7 (6.7), Valproic acid: 7.0 (6.6)	6 weeks	Valproic acid, n = 28	Placebo n = 28	BPRS, CMAI, Overt Aggression Scale	Moderate
Hermann, 2007	Long term care homes, Canada	85.6 (4.5)	MMSE 4.5 (4.6)	6 weeks, crossover with 2-week washout	Valproic acid, n = 14	Placebo n = 14	CMAI, NPI	Moderate
Sival, 2002	Psychogeriatric ward, Netherlands	80.4 (6.8)	MMSE: 11.4 (5.0)	Total treatment period: 3 weeks, 1 week baseline, 3 weeks treatment/placebo 2-week washout	Valproic acid, n = 43	Placebo n = 43	SDAS-9, CGI	Low
Tariot, 2001	Nursing homes, USA	Drug: 83.1 (6.67), Placebo: 83.6 (7.45)	MMSE, Drug: 7.1 (0.75), Placebo: 7.7 (0.77)	6-week parallel group	Valproic acid n = 87	Placebo n = 85	BMRS, CMAI, CGI, Secondary: Safety and tolerability	High
Tariot, 2005	Nursing home residents, USA	Drug: 84.2 (6.6), Placebo: 83.9 (5.9)	MMSE: Drug: 10.5 (4.9), Placebo: 10.8 (5.4)	6 weeks parallel design	Valproic acid: n = 75	Placebo: n = 78	BPRS, CMAI, MMSE, Safety and tolerability	Low

While carbamazepine has been studied in four trials, the overall quality of evidence is low. The largest trial with 51 participants and a positive result ended early due to an interim analysis, which may have overestimated the result.[35] All trials were limited by small sample sizes and reporting was incomplete in three of the five trials for which data could be abstracted. Moreover, follow-up periods ranged from 4 to 12 weeks, a period that is too short for accurately ascertaining the efficacy and safety of treatments for BPSD. Furthermore, methods for handling missing data were poorly described and differential loss to follow-up was observed in the trial of oxcarbazepine. There were insufficient data to determine the relative efficacy and safety of anticonvulsants in different populations of individuals with BPSD (e.g., community dwelling, long-term care, type of dementia), and few trials captured information on secondary outcomes such as adverse effects and caregiver- or patient-related impacts (e.g., caregiver burden). The low quality of available literature and the associated high risk of bias precludes drawing firm inferences about the efficacy and safety of non-benzodiazepine anticonvulsants for the treatment of BPSD.

DISCUSSION

We found six trials and one systematic review evaluating the efficacy and safety of carbamazepine, valproate preparations, oxcarbazepine and topiramate as treatment of BPSD in dementia. Although carbamazepine was evaluated in four trials, these were limited by insufficient power and incomplete outcome reporting, precluding our ability to conduct a meta-analysis and draw conclusions about the efficacy and safety of this drug. Five trials of valproate preparations were summarized in a recently updated systematic review, which found moderate quality of evidence for little to no effect of these drugs. The evidence base for topiramate and oxcarbazepine was limited to one trial for each drug, and we did not identify trials of other agents used in anxiety or mood disorders, such as gabapentin and pregabalin. Overall, the evidence is not sufficiently robust to recommend the use of anticonvulsants in the treatment of BPSD in dementia. Although our findings align with past reviews on this topic addressing individual groups, we have updated and summarized the

findings and quality of the available evidence using established systematic review methods.

Our review has important implications for clinical practice. Behavioral symptoms in dementia are a complex cluster of symptoms of varied etiology and definition. Specifically, such symptoms may reflect factors such as patient personality, neurodegeneration, co-existing symptoms, caregiver traits and interactions, and the environment or setting in which the patient resides. In this context, it is perhaps not surprising that the evidence supporting pharmacologic approaches to managing behavioural symptoms is weak, given that drug therapy alone is unlikely to address the many underlying factors contributing to behavioural symptoms in individuals with dementia. Moreover, there are ethical considerations and other challenges when conducting randomized trials of psychotropic medication for agitation in BPSD, including the use of placebos relative to active comparators that may mitigate symptoms. Although the evidence for antipsychotics and antidepressants is generally more robust than that for anticonvulsants, these agents would similarly be of limited use if the onset of behavioural symptoms is related to factors not amenable to treatment with these drugs. Consequently, given the multifactorial etiology of BPSD, there is likely no single "magic bullet" for mitigating these symptoms.[36] Instead, a suite of interventions comprising drug and non-drug therapies is needed to provide person-centred therapy customized to addressing the factors contributing to BPSD in each individual.[37] Notably, a recent systematic review and network meta-analysis concluded that nonpharmacologic interventions appeared more effective than drug therapy for BPSD.[18] Future work evaluating whether pharmacologic therapy can augment the benefits of non-pharmacologic approaches and defining which patients would benefit from drug therapy is needed.

Our systematic review has some limitations. We amended the protocol to include high quality systematic reviews. Specifically, as a well-done systematic review and meta-analysis was available for valproate preparations, we abstracted the information from the review rather than replicate this work. In addition, given the small number of trials identified, we included a trial that used DSM III diagnosis of dementia and other trials that used outcome measures not specifically mentioned in the protocol, such as the RAGE scale and the ward behavior rating scale. We could not conduct a meta-analysis of the abstracted data because of incomplete reporting, heterogeneity in outcome ascertainment and the limited number of trials available for oxcarbazepine and topiramate.

Some limitations were related to the current availability level of evidence. None of the trials reported on the effect of these medications on caregiver burden outcomes in the community or time to placement in LTC which are important outcomes. We did not identify any trials that differentiated treatment effects by type of dementia. Most of the trials were 6 weeks with the range being 4−12 weeks in duration. As BPSD duration is not limited to a few weeks and varies from weeks to months, short trials may not accurately represent effects over the actual course of the symptoms. Some anticonvulsants were not evaluated at all and the risk of bias in the summarized trials is substantial. In addition, the participants included in the trials were frail and with advanced dementia. The available evidence is therefore not generalizable to younger adults, those with early-stage dementia or healthier individuals who are living independently in the community. Moreover, there are no studies exploring heterogeneity in treatment efficacy or safety according to patient demographic characteristics, including race and ethnicity.

CONCLUSIONS

In summary, we found that anticonvulsants are generally not effective treatments for BPSD and that they may be associated with a higher prevalence of adverse events. However, the quality of the extant literature is low. Future studies of anticonvulsants in BPSD should address concerns about study quality identified in our review. Further, trials of other anticonvulsants, such as pregabalin or gabapentin, are needed to understand the risks and benefits of these drugs in patients with BPSD.

AUTHOR CONTRIBUTIONS

Sophiya Benjamin: *Conceptualization, Methodology, Title and full text screening, Data extraction, Analysis, Writing. This project was completed as part of the Duke-NIH Clinical Research Training Program, Masters in Health Sciences* ***Joanne MW Ho:*** *Title and full text screening, review of methodology, manuscript review;*

Jennifer Tung: *Title and full text screening, Data extraction, Manuscript review* ***Saumil Dholakia****: Title and full text screening, Data extraction, Manuscript review;* ***Howard An****: Title and full text screening,* ***Tony Antoniou****: Manuscript editing and review;* ***Stephanie Sanger:*** *Search Strategy, Database searches, Updates of searches as needed;* ***John Williams Jr****: Review and input into methodology, Manuscript review and editing.*

DATA STATEMENT

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DISCLOSURES

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