ORIGINAL ARTICLE

Safety, tolerability, and efficacy outcomes of the Investigation of Levetiracetam in Alzheimer's disease (ILiAD) study: a pilot, double-blind placebo-controlled crossover trial

Arjune Sen[1,2,3] | Sofia Toniolo[2,3] | Xin You Tai[1,2,3] | Mary Akinola[4] | Mkael Symmonds[1,3,5] | Sergio Mura[6] | Joanne Galloway[7] | Angela Hallam[8] | Jane Y. C. Chan[9,10] | Ivan Koychev[11] | Chris Butler[12] | John Geddes[11] | Gabriel Davis Jones[1,13] | Younes Tabi[14] | Raquel Maio[3] | Eleni Frangou[15,16] | Sharon Love[15,16] | Sian Thompson[2] | Rohan Van Der Putt[17] | Sanjay G. Manohar[2,3] | Rupert McShane[11] | Masud Husain[2,3,18]

Correspondence
Arjune Sen, Oxford Epilepsy Research Group, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford, UK.
Email: arjune.sen@ndcn.ox.ac.uk

Abstract

Objective: To assess whether the antiseizure medication levetiracetam may improve cognition in individuals with Alzheimer's disease who have not previously experienced a seizure.

Methods: We performed a randomized, double-blind, placebo-controlled crossover pilot study in individuals with mild-to-moderate Alzheimer's disease. Electroencephalography was performed at baseline and those with active epileptiform discharges were excluded. Eligible participants were randomized to placebo for 12 weeks or an active arm of oral levetiracetam (4 weeks up-titration to levetiracetam 500 mg twice daily, 4 weeks maintained on this dose followed by 4 weeks down-titration to nil). Participants then crossed over to the other arm. The primary outcome was change in cognitive function assessed by the Oxford Memory Task, a task sensitive to hippocampal memory binding. Secondary outcomes included tolerability, other neuropsychological scales, and general questionnaires.

Results: Recruitment numbers were severely limited owing to restrictions from the COVID-19 pandemic at the time of the study. Eight participants completed both arms of the study (mean age 68.4 years [SD = 9.2]; 5 females [62.5%]). No participants withdrew from the study and there was no significant difference between reported side effects in the active levetiracetam or placebo arm. Measures of mood and quality of life were also not significantly different between the two

For affiliations refer to page 10.

arms based on participant or carer reports. In limited data analysis, there was no statistically significant difference between participants in the active levetiracetam and placebo arm on the memory task.

Significance: This pilot study demonstrates that levetiracetam was well tolerated in individuals with Alzheimer's disease who do not have a history of seizures and has no detrimental effect on mood or quality of life. Larger studies are needed to assess whether levetiracetam may have a positive effect on cognitive function in subsets of individuals with Alzheimer's disease.

Plain Language Summary: Abnormal electrical activity within the brain, such as is seen in seizures, might contribute to memory problems in people with dementia. We completed a clinical trial to see if an antiseizure medication, levetiracetam, could help with memory difficulties in people with Alzheimer's disease (the most common cause of dementia). In this pilot study, we could not prove whether levetiracetam helped memory function. We did show that the drug is safe and well tolerated in people with dementia who have not had a seizure. This work, therefore, offers a platform for future research exploring antiseizure medications in people with dementia.

KEYWORDS

antiseizure medications, dementia, epilepsy, Oxford Memory Test, seizure

1 | INTRODUCTION

The burgeoning healthcare needs of dementia threaten to overwhelm healthcare systems around the world. In the United States, for example, there are estimated to be over 6 million people living with dementia leading to a current cost of over 345 billion dollars.[1] Over the next 40 years it is predicted that there will be around 13 million people with Alzheimer's disease (AD) in the United States alone with most of this increase occurring in people aged over 85 years. Dementia prevalence is also increasing in low to middle-income countries where populations are aging three times faster than in the global west.[2] In such resource-under-privileged regions the direct and indirect impacts of dementia are vast and it will be very difficult for people living in such settings to access highly specialized and expensive medicines that may only offer modest improvements in cognitive function.

Epilepsy also increases as populations age with its greatest incidence in those over 75 years of age. Although it has been recognized for many decades that seizures are more common in people with dementia,[3] until recently this has been considered an epiphenomenon—a simple consequence of neuronal loss destabilizing neuronal networks. Over the past decade, several lines of enquiry have demonstrated that there is a bidirectional relationship between epilepsy and dementia.[4–6] It seems likely that seizures or

> **Key points**
>
> 1. Epilepsy may contribute to the etiopathogenesis of Alzheimer's disease.
> 2. ILiAD is a double-blind, randomized placebo-controlled trial of levetiracetam in Alzheimer's disease.
> 3. Levetiracetam was well tolerated in people with AD who have not had a seizure.
> 4. Owing to small sample size, effect of levetiracetam on cognition could not be determined.
> 5. Larger trials of antiseizure medications in people with dementia are warranted.

epileptic activity in the aging brain may contribute to the pathogenesis of AD.[7–10] Importantly, epilepsy can often be treated with cheap, generic antiseizure medications (ASMs).[11] The inter-linking of epilepsy and dementia, therefore, raises the possibility that suppression of abnormal epileptic activity may help cognition in those with AD.

Antiseizure medications have been explored in animal models of AD with a particular focus on the synaptic vesicle 2A antagonist levetiracetam.[12] Levetiracetam can reduce neuritic plaque formation[13] and suppress abnormal

electrical activity in animal models of AD. In transgenic mice, levetiracetam also associates with amelioration of cognitive and behavioral deficits.[12] In humans with mild cognitive impairment, suppression of aberrant hippocampal hyperactivation resulted in better performance on a visual recognition task.[14] Also, levetiracetam is a widely utilized ASM with minimal drug–drug interactions and demonstrated efficacy and tolerability in older people.[15] It, therefore, would seem worthwhile considering whether levetiracetam offers benefit to people with dementia who have *not* previously experienced a seizure.

The Investigation of Levetiracetam in Alzheimer's disease (ILiAD) trial was designed as a randomized, double-blind, placebo-controlled crossover study. The primary endpoint was change in cognitive function assessed through a highly specific hippocampal binding task. Secondary endpoints included adverse effects, impact on mood, quality of life assessments, and evaluation of electroencephalographic recording to try and predict drug response. Regrettably, the COVID-19 pandemic affected the study very adversely and the trial, which by definition was in a vulnerable older population, had to be halted early. Here we present the data of all participants who completed the study with specific emphasis on how similar studies can be developed in future.

2 | METHODOLOGY

2.1 | Main trial outline

The methodology underpinning the ILiAD trial—a proof-of-concept pilot study—(registration number: NCT03489044) has been published previously.[16] In brief, people aged over 50 years with a confirmed diagnosis of mild-to-moderate AD, who had not experienced an overt seizure, were invited to participate. A diagnosis of AD was made according to McKhann's criteria encompassing an individual's clinical phenotype and supportive investigations including brain magnetic resonance imaging (MRI) and ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET).[17]

Participants were recruited from Oxford University Hospitals NHS Foundation Trust and Oxford Health Foundation Trust. The clinical team made initial approaches. All participants had to have capacity to provide informed consent and had to have a named carer who would assist with trial procedures. Based on power calculations (90% power at a 5% significance level),[16] a total of 24 participants would be needed to detect a meaningful difference on the OMT. To account for an attrition rate of up to 20%, we planned to recruit 30 participants.

Potentially suitable candidates underwent initial screening that included checks of renal function, baseline cognitive assessment and an electroencephalogram (EEG). Full inclusion and exclusion criteria are listed in Table S1. People with epileptiform abnormalities on EEG recording were specifically excluded as was anybody who was taking an ASM for any reason (for example gabapentin being taken for pain). These strict criteria were applied so that levetiracetam was not simply treating seizure activity and any potential impact on neural networks was not masked/modulated by other ASMs.

Consenting participants who met all inclusion and exclusion criteria were enrolled into the study and, using a restricted block randomization method, randomized 1:1 to begin with levetiracetam or placebo. Randomization codes were generated by the Centre for Statistics in Medicine, University of Oxford. Potential participants were initially approached by their direct clinical care team. Eligible participants were then enrolled and allocated to interventions by the ILiAD research team.[16]

Levetiracetam (250 mg tablets) and placebo were manufactured to look identical and carers dispensed tablets according to a specifically created treatment chart.[16] For those allocated to receive active drug first, levetiracetam was up-titrated by 250 mg (one tablet) every week for 4 weeks before being maintained at levetiracetam 500 mg (two tablets) twice daily for 4 weeks. Levetiracetam was then down-titrated to nil over 4 weeks. People subsequently crossed over to the placebo arm where a similar titration schedule was completed. For those initially allocated to the placebo arm the titration schedule was identical except that placebo was up-titrated and weaned first, followed by the crossover to active drug.

The trial flowsheet (Figure 1) was identical for all participants. Key assessment points were at baseline, 8 weeks (after completion of 4 weeks on active drug/placebo in arm 1), and 20 weeks (after completion of 4 weeks on active drug/placebo in arm 2). Intra-participant measures were evaluated and group analyses performed. All parties—participants, carers, assessors, and clinicians—were blinded as to study outcome until study closure.

2.2 | "What was where?" Oxford memory task—Primary outcome measure

The ILiAD study used a modified version of the "What was where?" Oxford Memory Task (OMT).[18–24] This task is sensitive to early signs of working memory deficits in individuals with hippocampal dysfunction such as patients with limbic encephalitis,[18] previous temporal lobe lobectomy,[24] familial Alzheimer's AD,[19,23] late-onset sporadic AD[20,22] and subjects at risk of developing AD.[20,22] The OMT can detect early impairment in
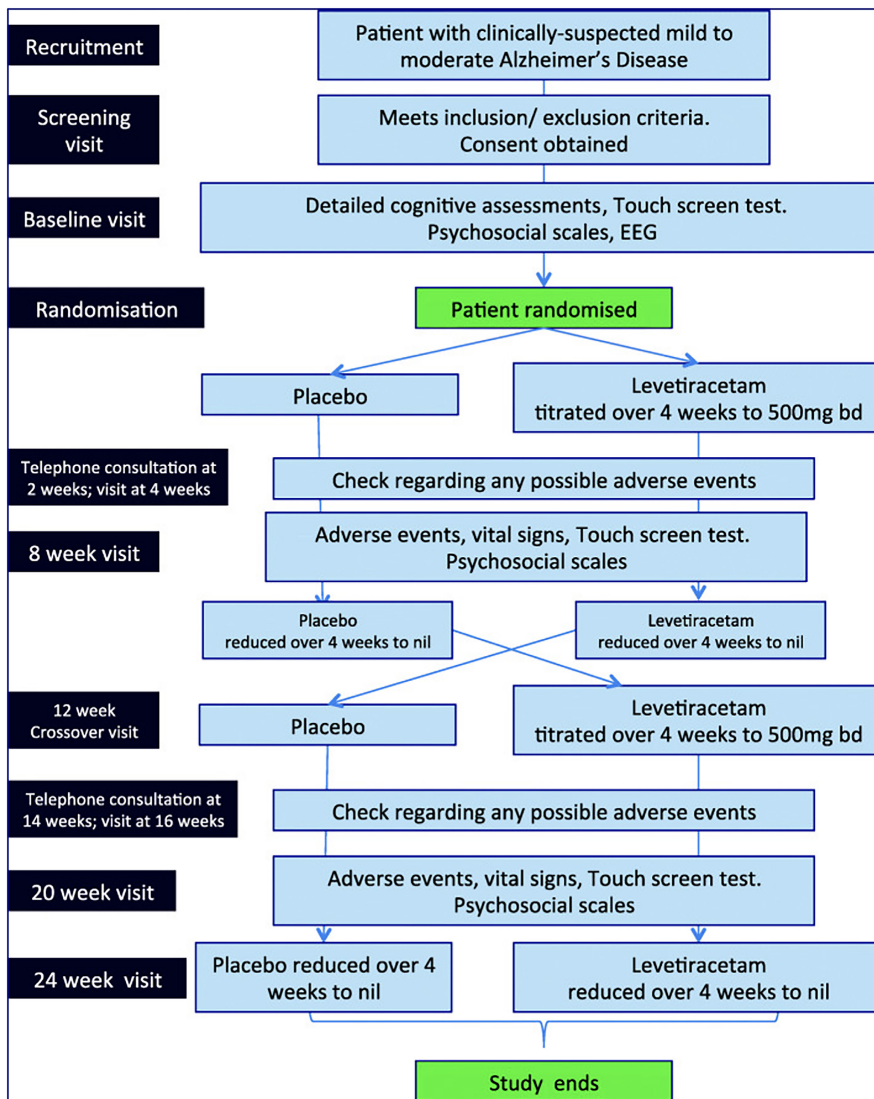
FIGURE 1 Schema for the ILiAD trial. ILiAD trial flowsheet from recruitment through crossover and monitoring (adapted from[16]) After baseline assessments, recruited participants were randomized to first receive either levetiracetam or placebo. Detailed assessments were performed at 8 weeks to compare to baseline data. After weaning away levetiracetam/placebo, participants crossed over to the second arm and received the opposite of what they had been given in the first arm (namely people receiving levetiracetam now received placebo and vice versa). Assessment at 20 weeks was compared to data acquired at 12 weeks and levetiracetam/placebo was then down-titrated to nil by 24 weeks.

memory binding even when overall performance is still intact.[18,24]

During the task, participants were presented with either one (*Fractals 1*) or two (*Fractals 2*) fractals located randomly on the black screen (Figure 2). Participants were asked to remember the design of the fractal(s) shown ('what'), and their locations ('where'). After a 4-s blank screen delay, two fractals appeared at the center of the screen along the vertical midline. One of these fractals was present in the previous array (target) while the other fractal was new (distractor). Participants were asked to touch the target fractal and drag it to the original location. Trial order was randomized within each block and fractal location was pseudorandomized, based on a MATLAB script (MathWorks, Inc).

Stimuli were presented on a black background and were chosen from a library of 196 fractals (http://sprott.physics.wisc.edu/fractals.htm). Participants sat approximately 30 cm in front of a tablet (either iPad or Android), yielding 2.3° of visual angle. Stimuli were calibrated using

the dimension on the screen to ensure matching of stimuli properties across different tablet models.

Several primary working memory metrics can be determined from the OMT (Figure 2), including:

- **Identification Time**: the time in seconds taken to identify the correct object.
- **Localization Time**: the time in seconds to drag the chosen object to its remembered location.
- **Proportion correct**: the proportion of trials in which participants correctly identified the target.
- **Absolute Error**: the distance from the center of original item location to the center of participant's response location.

In the two-item condition (Fractals 2), further metrics can be derived based on the Mixture Model of working memory by Bays and colleagues,[25] adapting the original model by fitting the data to different memory outcome distributions using a permutation approach, described
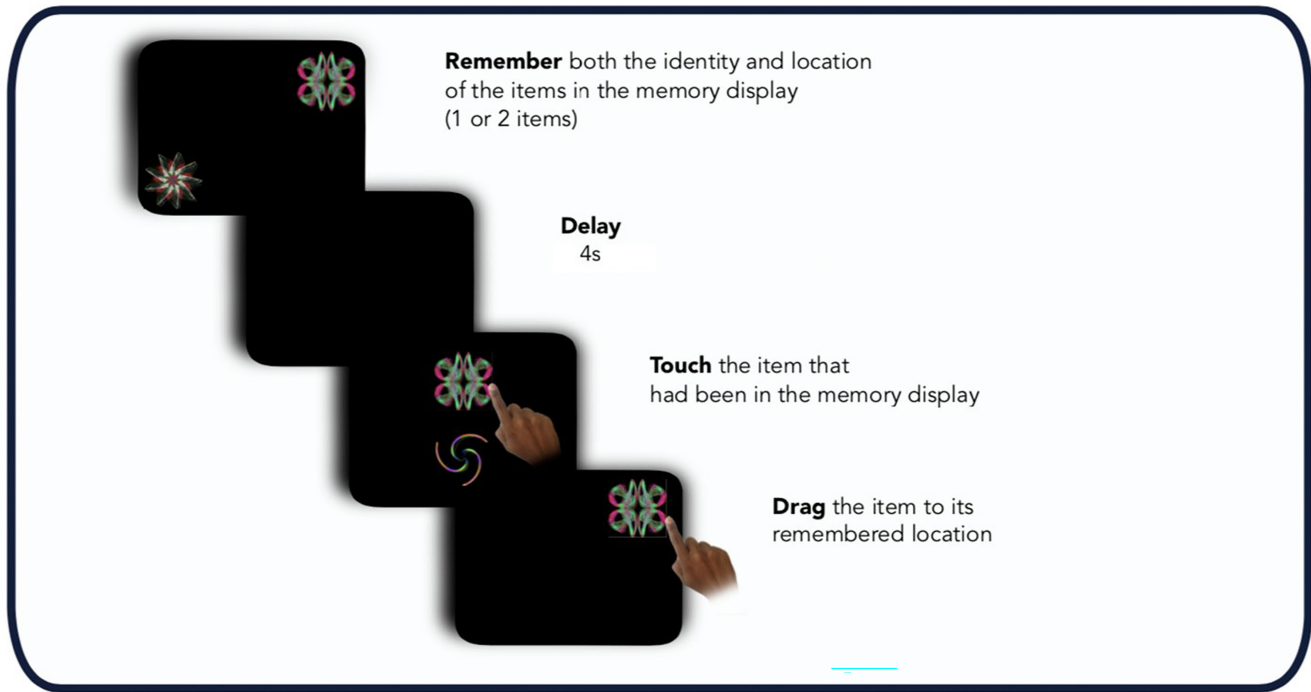
FIGURE 2 "What was where?" Oxford Memory task (OMT). Participants were presented with either 1 or 2 fractals randomly distributed on the screen. After a 4 s delay two fractals appeared at the center of the screen, one of which had appeared in the memory array whereas the other one was a distractor. Firstly, they needed to identify the object they had seen previously ('what'), and then drag it back to its original location ('where').

further in Figure S1. This approach has been previously published using this task.[22,26]

- **Target detection**: the probability of correctly identifying the target.
- **Guessing**: the probability of random guessing responses.
- **Misbinding**: the probability of mislocalizing correctly identified item to the remembered location of another item in the memory array.
- **Imprecision**: the width of the distribution of the responses around the target.

2.3 | Neuropsychological tests, questionnaires, and scales

The tests and questionnaires administered during ILiAD included the Mini Mental State Examination (MMSE),[27] Bristol Activity of Daily Living Scale (BADLS),[28] Dementia Severity Rating Scale (DSRS),[29] Neuropsychiatric Inventory (NPI),[30] Euro-Qol Quality of Life measure (EQ5D),[31] and Quality of life scale (QoL).[32] QoL scales included a patient version (patient responded regarding his/her quality of life) and a caregiver version (caregiver responding on their quality of life). EQ5D scales included a patient version, a caregiver version, and a proxy version (caregiver responding on the patient's estimated quality of life).

2.4 | Electroencephalography recording

A baseline EEG was performed for all potential participants, principally to exclude the presence of epileptiform activity. Recordings were obtained via scalp electrodes, individually attached according to the international 10–20 system, following the local hospital protocols.

2.5 | Adverse effect reporting

Levetiracetam, as outlined, is a well-tolerated and widely prescribed antiseizure medication and is a drug of choice in older people with epilepsy. The safety and tolerability profile of levetiracetam is well-established. A full description of our adverse event reporting and harms protocol has been provided previously with principal potential adverse events listed in Table S2.[16]

2.6 | Statistical analyses

As outlined in the ILiAD research protocol[16] (Figure 1), changes in questionnaire responses were calculated by comparing the change from the end of each arm of the study to its baseline, that is, week 8 compared to baseline (arm 1) and week 20 compared to week 12 (arm 2). For demographics and baseline cognitive tests (MMSE), a two-sample *t* test

or Mann–Whitney U test were used to compare continuous variables, according to the normality of the data. The chi-square test was used to compare categorical variables. Paired t-test and Wilcoxon signed-rank test were used to compare questionnaires' measures between the two arms of the study, according to the normality of the data.

Given the final small sample size, which was not anticipated when conceiving the study, for the computerized metrics we fitted a within-subject linear mixed effect model, as is standard practice in experimental psychology for experiments with small number of participants studied under two or more experimental conditions.[33] The inter-individual variability was taken into account by including trial by trial data (20 trials per session) for each individual and by considering each participant uniquely in the model, while looking at the separate effects of session (by comparing the first and the second session) and the effect of drug (placebo or levetiracetam) across subjects. For each outcome variable, the following model was fitted: var. $\sim 1 +$ session $\times$ drug $+ (1|$subject$)$. Significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Randomization

ILiAD opened in November 2019 and had to close to recruitment owing to the COVID-19 pandemic in March 2020. Prior to having to halt the trial, 8 participants were recruited. No participant was unblinded for clinical purposes before the end of the trial. All participants completed the entire study—both arms. Owing to the pandemic, though, the trial had to be adapted and certain tasks that required in-person assessments could not be completed. Baseline EEG was performed for all participants. In four individuals periods of light sleep were captured and for one of those participants, sleep associated with bursts of slow wave activity over fronto-central regions. In an additional participant drowsiness was recorded and that individual's EEG demonstrated some irregular slow activity, more over the left hemisphere than the right. Of the eight participants, four had FDG-PET data available.

At the end of the study, unblinding revealed that 3 individuals were allocated to the arm where placebo was given first, and 5 to the arm where levetiracetam was given first (Table 1).

3.2 | Demographics

There was no difference between participants in the two arms (people started on levetiracetam first vs. placebo first) in terms of age, sex, or baseline MMSE (Table 1). As the trial was interrupted owing to the COVID-19 pandemic and given the necessary face-to-face nature of the MMSE test, this was administered only at baseline. All participants completed the other questionnaires and scales remotely until the end of the study (week 24).

The "What was where?" OMT also required in-person assessment. For the OMT, data collection was interrupted at different stages of enrolment (Table 1). Datapoints of the OMT task from week 12 onwards were excluded from further analyses as none of the participants completed the task at week 20. Data from those with only OMT assessment at baseline were also excluded from further analyses. As a result, the samples for assessment of the primary endpoint compared where $n = 2$ per arm with 2 timepoints per arm.

TABLE 1 Demographics overview.

	Overall (n = 8)	PLACEBO first (n = 3)	LEV first (n = 5)	p-value
Age	68.4 (9.2)	70.3 (6.0)	67.2 (11.2)	n.s.
Sex (M/F)	3/5	0/3	3/2	n.s.
MMSE	17.7 (4.5)	15.3 (3.2)	19.2 (4.8)	n.s.
Dropout/withdrawn	0/8	0/3	0/5	
Questionnaires– 20 weeks	8/8	3/3	5/5	
OMT – Baseline	8/8	3/3	5/5	
OMT – 8 weeks	4/8	2/3	2/5	
OMT – 12 weeks	3/8	2/3	1/5	
OMT – 20 weeks	0/8	0/3	0/5	

Note: Values are presented as mean, with standard deviation (SD) in brackets. The different OMT timings reflect the four different timepoints where OMT was scheduled in the trial, with the relative number of subjects completing the OMT test at each timepoint.

Abbreviations: F, female; LEV, Levetiracetam; M, male; MMSE, Mini mental state examination; n. s., not significant; OMT, "What was where?" Oxford Memory task.

3.3 | Primary outcome: "What was where?" Oxford memory task (OMT)

Overall, there was no statically significant difference in the metrics examined between participants in the two arms (started on levetiracetam first or placebo first) for Fractals 1 (Figure 3, Table 2), and Fractals 2 (Figures S2 and S3, Table S3). The very small numbers, though, do not allow firm conclusions on this.

3.4 | Secondary outcomes

3.4.1 | Safety and tolerability outcomes

Study dropouts and missing doses
No participants withdrew from the study. One participant delayed increasing from one tablet to two tablets by 3 days due to a participant query. After a telephone consultation, it was deemed suitable to continue the participant in the study, and the dose was increased up to the target dose. No other missing doses neither reported at any time by any other participants nor revealed by the drug administration chart.

3.4.2 | Neuropsychological scales and questionnaires

Measures of mood, activity of daily living, dementia severity, and quality of life
There was no statically significant difference between placebo and levetiracetam in measures of mood (NPI), activity of daily living (BADLS), dementia severity (DSRS), and quality of life (QoL, EQ-5D, DSRS), whether reported by the patient, by the caregiver, or if estimated by the caregiver with respect to the patient (Figure S4).

3.4.3 | EEG recordings

Baseline EEG recordings were assessed by a consultant neurophysiologist (MS) for any clinically relevant
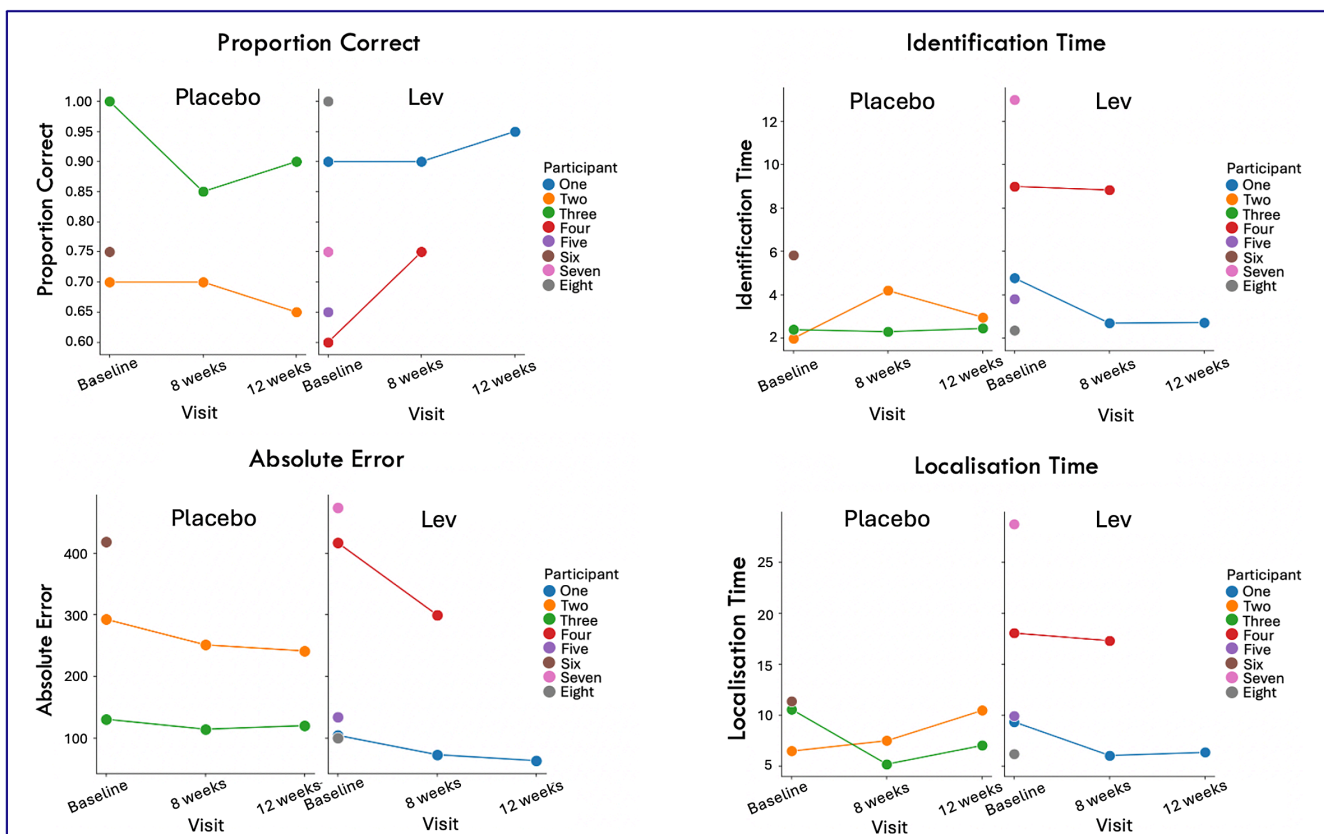

FIGURE 3 Individual datapoints for Fractals 1 testing. Values are presented as color-coded individual datapoints, for all subjects who took part in the study. Randomization status is represented by different subplots for each metric (left for placebo, right for levetiracetam). Lev = levetiracetam. Proportion correct = proportion of correctly identified items. Identification time = time in seconds identify the correct object. Absolute Error = distance between the original item location to the participant's response location. Localization Time = the time in seconds to drag the chosen object to its remembered location. Higher values correspond to better localization for proportion correct, and to worse performance for absolute error, identification, and localization time.

TABLE 2 Fractals 1 results.

	Coefficients	Standard error	*t*-value	*p*-value
Fractals 1				
Proportion correct				
Session	−0.07	0.089	−0.84	0.40
Drug	−0.25	0.20	−1.23	0.21
Session × drug	0.15	0.13	1.20	0.24
Absolute error				
Session	−22.46	34.13	−0.66	0.51
Drug	97.55	116.6	0.84	0.40
Session × drug	−60.70	48.3	−1.26	0.21
Identification time				
Session	−505.53	2251.2	−0.22	0.82
Drug	10 033	3183.7	3.15	0.002
Session × drug	−4696.3	2013.5	−2.33	0.02

Note: Session = baseline or 8 weeks, Drug = randomization allocation (whether on placebo or levetiracetam), Session × drug = interaction between session and drug, that is, whether being on the levetiracetam or placebo changed the cognitive outcome. p = p-value, with statistical significance set at $p < 0.05$. The significant results for session × drug interaction for identification time did not survive multiple comparisons' correction.

findings. There was no evidence of epileptiform activity in any study participants. Planned further analyses of baseline EEG to predict response was not performed owing to the small numbers recruited.

3.4.4 | Adverse events reported

There were 35 adverse instance reports that ranged from "fatigue" (three instances) to "word finding difficulty" (two instances). "Headache" was the most frequently reported symptom with 11 instances (Figure S5). There were no suspected unexpected serious adverse reactions (SUSARs) reported.

Three of the eight study participants accounted for 33 out of 35 adverse instance reports. Of these reports, 19 were made while the participants were taking placebo and 16 were reported during while the participant was on levetiracetam (Figure 4). Amongst our 8 participants, there was no difference in number of adverse reporting instances between active and non-active arms of the study ($t = −0.243$, 95% CI: −8.32 to 6.82, $p = 0.82$).

4 | DISCUSSION

In this proof-of-concept study, we assessed the safety and tolerability of levetiracetam in patients with AD without overt seizures or baseline epileptic EEG activity, and the effect of levetiracetam on cognition. Regrettably, we were not able to complete recruitment owing to the COVID-19 pandemic.
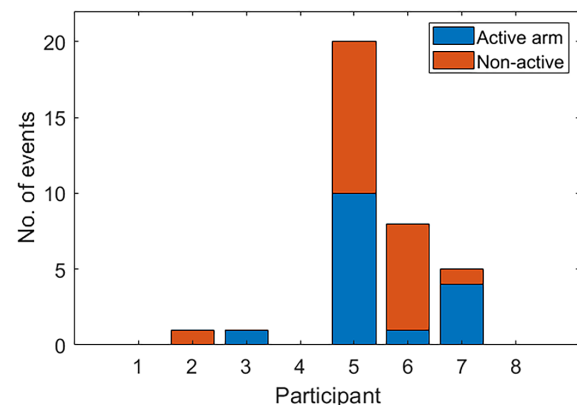

FIGURE 4 Number of adverse reporting instances. Four study participants accounted for all the adverse reporting instances in the active arm of the study. Nineteen adverse instances were reported while participants were in the non-active, placebo arm (red) of the study, and 16 were reported during the active, levetiracetam arm (blue).

The main result of this trial is that levetiracetam was well tolerated in our cohort of eight older people with AD who have not experienced a seizure. No participant withdrew from the study prematurely. The adverse effects were mild, in line with known side effects of levetiracetam[34] and there was no difference in the rate of side effects when comparing levetiracetam to placebo. Importantly, there was no worsening of mood in the levetiracetam arm compared to the placebo arm, both in terms of self-reported adverse effects and objective measures such as the NPI. This reinforces previous data showing levetiracetam as a

safe and well-tolerated drug in older people,[34–38] and extends these findings specifically to individuals with AD. Measures of quality of life were not statistically different in the two arms, with evidence of both increase and decrease in quality of life in patients and caregivers on placebo and levetiracetam. Further studies are needed to investigate whether more definite trends could be detectable with a higher sample size.

We did not have sufficient data to assess the primary outcome of the study, the effect of levetiracetam on cognition, measured by our computerized cognitive task. The hippocampal binding task deployed here was deliberately chosen owing to low practice effect. Standard auditory verbal learning tests using word lists, such as the Rey Auditory Verbal Learning Test, are good indices of episodic memory. Marked practice effects, though, can hinder their interpretation over short time intervals as employed in ILiAD.[39]

All participants were, able to complete the in-person computerized task when it was possible to run the test, with no incomplete data. As those recruited were primarily in a moderate stage of the disease, as indexed by the MMSE (Table 1), our data suggests that this computerized task can be a viable resource to quantify granular changes in cognition over a short time scale. Such tests measure working memory and are less susceptible to practice effects compared to traditional tests of cognition. Future trials in AD might consider similar cognitive testing strategies to substantially reduce trial length.

Titration of IMP in ILiAD was relatively brisk and levetiracetam was increased to 500 mg twice daily, higher than was employed in previous studies of MCI and a similar study in AD.[14,40] Our initial rationale was that people with AD are likely to have more network instability than those with MCI, hence a higher dose of levetiracetam might be required in AD. While we cannot comment on the effect of this higher dose on the primary outcome measure, it is serendipitous that we can show that there are no adverse neuropsychiatric effects from levetiracetam 500 mg twice daily compared to placebo. In future trials, a multi-arm strategy can be deployed to help optimize levetiracetam dosing in people with dementia.

A similar, independent study was run concurrently with the ILiAD trial to address whether levetiracetam could improve executive function in patients with Alzheimer's disease.[40] In that American cohort, 34 individuals with Alzheimer's disease completed a similar double-blind, crossover study design with a substantially lower dose of levetiracetam (125 mg twice daily). That study's primary endpoint was not met as no overall difference in cognitive outcomes were detected with levetiracetam compared to controls. Nine patients, however, who had detectable epileptiform activity on their baseline EEG, showed a small improvement on a Stroop test subscale and virtual route learning test at the group level suggesting a potential domain-specific improvement in executive skills.[40] Consistent with the ILiAD trial, there were no safety concerns reported.[40]

As outlined, participants with epileptiform activity were excluded from ILiAD. Suppression of seizures is the first step to helping cognitive function in those with epilepsy. Given that AD so closely associates with seizure disorders, it is possible that people with AD and epileptiform activity on EEG recording have experienced unrecognized seizures and that, therefore, in that sub-population levetiracetam is simply treating a hitherto unrecognized epilepsy.

Interictal epileptiform discharges may also be indicative of the increasingly apparent hyperexcitable network dysfunction seen in AD.[41] Moving forward, larger studies should stratify participants by EEG signature and evaluate the effect of treatments on EEG as a potential biomarker of therapeutic effect. Already, though, these two innovative trials exploring ASMs as a therapy in dementia offer a new avenue to trying to improve cognitive function in AD and confirm that levetiracetam is a safe medication in this patient cohort.

5 | LIMITATIONS

Limitations of this study are primarily driven by the premature interruption of the trial, which resulted in a small number of individuals being recruited (8 compared to 30 planned) and lack of completion of the computerized cognitive tasks (only 2 subjects per arm and only 2 timepoints per arm). Since the inception of ILiAD we have developed a fully remote version of the "What was where?" Oxford Memory task,[42] which is now available at https://oxfordcognition.org/. In this way, our computerized cognitive assessment can now be performed regardless of the nature of the visit (remote or in-person). This new version of the OMT is deployable across devices (computers, tablets, and mobile phones), thus resulting in higher scalability of future, possibly multicentric clinical trials.

The small sample number and lack of being able to test the primary endpoint, also meant several subsidiary analyses could not be performed—for example whether analysis of the EEG might provide a biomarker for who could benefit most from levetiracetam therapy.

While disappointing that such hypotheses could not be tested, the effort and reorganization involved to continue a trial in one of the most vulnerable groups (older people with AD) during the COVID-19 pandemic cannot be underestimated. Many researchers were redeployed to

COVID studies or other clinical roles and it is testament to the participants recruited that all individuals completed the study even though there were so many changes to testing and, for example, delivery of IMP.

6 | CONCLUSION

These pilot data show that levetiracetam is well tolerated in patients with AD who have not have seizures and has no detrimental effect on mood or quality of life. Larger studies should be very actively explored to assess whether levetiracetam may have a positive effect on cognitive function in those with AD who have not experienced a seizure. Given the rapid increase of people with dementia in low to middle income countries, particular emphasis should be given to trialing levetiracetam in these resource underprivileged settings.

AUTHOR CONTRIBUTIONS

Arjune Sen conceptualized, initiated and was chief investigator for the trial. Sofia Toniolo, Xin You Tai, Mary Akinola, Mkael Symmonds, Sergio Mura, John Geddes, Ivan Koychev, Sian Thompson, Rohan Van Der Putt, Sanjay G Manohar, Rupert McShane, Masud Husain were all responsible for recruitment and data acquisition. Sergio Mura, Joanne Galloway were the clinical trial pharmacists. Angela Hallam was responsible for dispensing active drug and placebo. Sofia Toniolo, Xin You Tai, Gabriel Davis Jones, Younes Tabi, Raquel Maio were involved in analysis of data, this being led by Sofia Toniolo and Xin You Tai. Arjune Sen, Ivan Koychev, Jane Y C Chan, Chris Butler, John Geddes, Sanjay G Manohar, Rupert McShane, Masud Husain provided strategic oversight through the study. Arjune Sen, Sofia Toniolo, and Xin You Tai drafted the manuscript. Other listed co-authors reviewed and commented on the draft manuscript.

AFFILIATIONS
[1]Oxford Epilepsy Research Group, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford, UK

[2]Department of Neurology, John Radcliffe Hospital, Oxford, UK

[3]Nuffield Department of Clinical Neuroscience, University of Oxford, Oxford, UK

[4]Local Clinical Trials Network, John Radcliffe Hospital, Oxford, UK

[5]Department of Clinical Neurophysiology, John Radcliffe Hospital, Oxford, UK

[6]Clinical Trials Pharmacy, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[7]CPSU, Oxford Health Foundation Trust, Oxford, UK

[8]St Mary's Pharmaceutical Unit, Cardiff University, Cardiff, UK

[9]Freeline Therapeutics, King's Court, Stevenage, UK

[10]Translational Medicine, UCB Pharma, Slough, UK

[11]Department of Psychiatry, University of Oxford, Oxford, UK

[12]Faculty of Medicine, Department of Brain Sciences, Imperial College, Sir Alexander Fleming Building, South Kensington Campus, London, UK

[13]Nuffield Department of Women's Health, Women's Centre, John Radcliffe Hospital, Oxford, UK

[14]Department of Neurology, University Hospital of Kiel, Kiel, Germany

[15]MRC Clinical Trials Unit at UCL, Faculty of Pop Health Sciences, Institute of Clinical Trials & Methodology, University College London, London, UK

[16]Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

[17]Memory and Cognition Research Delivery Team, Warneford Hospital, Oxford, UK

[18]Cognitive Neurology Research Group, Nuffield Department Clinical Neurosciences & Department of Experimental Psychology, University of Oxford, West Wing, John Radcliffe Hospital, Oxford, UK

CONFLICT OF INTEREST STATEMENT
None of the authors declare any personal direct conflicts of interest. The Oxford Epilepsy Research Group have received research monies from UCB Pharma, who provided active drug and placebo for this study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT
Raw data files will be made available on reasonable request.

ETHICAL APPROVAL
United Kingdom, Research Ethics Committee reference number: 17/SC/0468. Clinical trial registration: clinicaltrials.gov – NCT03489044. All participants were required to have capacity to consent to the ILiAD study and such consent was provided by all enrolled participants.

ORCID

Arjune Sen https://orcid.org/0000-0002-8948-4763
Sofia Toniolo https://orcid.org/0000-0002-1833-4995

REFERENCES

1. https://www.alz.org/alzheimers-dementia/facts-figures. Accessed February, 19 2024.

2. Martin Prince A, Wimo A, Guerchet M, Ali GC, Wu Y-T, Prina M. World Alzheimer Report 2015 the global impact of dementia an analysis of prevalence, incidence, cost and trends. https://www.alzint.org/resource/world-alzheimer-report-2015 Accessed March 31, 2024.

3. Hesdorffer DC, Hauser WA, Annegers JF, Kokmen E, Rocca WA. Dementia and adult-onset unprovoked seizures. Neurology. 1996;46(3):727–30. https://doi.org/10.1212/WNL.46.3.727

4. Sen A, Capelli V, Husain M. Cognition and dementia in older patients with epilepsy. Brain. 2018;141(6):1592–608. https://doi.org/10.1093/BRAIN/AWY022

5. Tai XY, Torzillo E, Lyall DM, Manohar S, Husain M, Sen A. Association of dementia risk with focal epilepsy and modifiable cardiovascular risk factors. JAMA Neurol. 2023;80(5):445–54. https://doi.org/10.1001/jamaneurol.2023.0339

6. Schnier C, Duncan S, Wilkinson T, Mbizvo GK, Chin RFM. A nationwide, retrospective, data-linkage, cohort study of epilepsy and incident dementia. Neurology. 2020;95(12):e1686–e1693. https://doi.org/10.1212/WNL.0000000000010358

7. Tai XY, Bernhardt B, Thom M, Thompson P, Baxendale S, Koepp M, et al. Review: neurodegenerative processes in temporal lobe epilepsy with hippocampal sclerosis: clinical, pathological and neuroimaging evidence. Neuropathol Appl Neurobiol. 2018;44(1):70–90. https://doi.org/10.1111/nan.12458

8. Tai XY, Koepp M, Duncan JS, Fox N, Thompson P, Baxendale S, et al. Hyperphosphorylated tau in patients with refractory epilepsy correlates with cognitive decline: a study of temporal lobe resections. Brain. 2016;139(9):2441–55. https://doi.org/10.1093/brain/aww187

9. Sen A, Thom M, Martinian L, Harding B, Cross JH, Nikolic M, et al. Pathological tau tangles localize to focal cortical dysplasia in older patients. Epilepsia. 2007;48(8):1447–54. https://doi.org/10.1111/J.1528-1167.2007.01107.X

10. Romoli M, Sen A, Parnetti L, Calabresi P, Costa C. Amyloid-β: a potential link between epilepsy and cognitive decline. Nat Rev Neurol. 2021;17(8):469–85. https://doi.org/10.1038/s41582-021-00505-9

11. Kanner AM, Bicchi MM. Antiseizure medications for adults with epilepsy: a review. JAMA. 2022;327(13):1269–81. https://doi.org/10.1001/JAMA.2022.3880

12. Sanchez PE, Zhu L, Verret L, Vossel KA, Orr AG, Cirrito JR, et al. Levetiracetam suppresses neuronal network dysfunction and reverses synaptic and cognitive deficits in an Alzheimer's disease model. Proc Natl Acad Sci USA. 2012;109(42):E2895–E2903. https://doi.org/10.1073/PNAS.1121081109/-/DCSUPPLEMENTAL

13. Shi JQ, Wang BR, Tian YY, Xu J, Gao L, Zhao S-L, et al. Antiepileptics topiramate and levetiracetam alleviate behavioral deficits and reduce neuropathology in APPswe/PS1dE9 transgenic mice. CNS Neurosci Ther. 2013;19(11):871–81. https://doi.org/10.1111/CNS.12144

14. Bakker A, Krauss GL, Albert MS, Speck CL, Jones LR, Stark CE, et al. Reduction of hippocampal hyperactivity improves cognition in amnestic mild cognitive impairment. Neuron. 2012;74(3):467–74. https://doi.org/10.1016/J.NEURON.2012.03.023

15. Cumbo E, Ligori LD. Levetiracetam, lamotrigine, and phenobarbital in patients with epileptic seizures and Alzheimer's disease. Epilepsy Behav. 2010;17(4):461–6. https://doi.org/10.1016/J.YEBEH.2010.01.015

16. Sen A, Akinola M, Tai XY, Symmonds M, Jones GD, Mura S, et al. An investigation of levetiracetam in Alzheimer's disease (ILiAD): a double-blind, placebo-controlled, randomised crossover proof of concept study. Trials. 2021;22(1):508. https://doi.org/10.1186/S13063-021-05404-4

17. McKhann G, Knopman D, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:263–9. https://doi.org/10.1016/j.jalz.2011.03.005

18. Pertzov Y, Miller TD, Gorgoraptis N, Caine D, Schott JM, Butler C, et al. Binding deficits in memory following medial temporal lobe damage in patients with voltage-gated potassium channel complex antibody-associated limbic encephalitis. Brain. 2013;136(8):2474–85. https://doi.org/10.1093/brain/awt129

19. Liang Y, Pertzov Y, Nicholas JM, Henley SMD, Crutch S, Woodward F, et al. Visual short-term memory binding deficit in familial Alzheimer's disease. Cortex. 2016;78:150–64. https://doi.org/10.1016/j.cortex.2016.01.015

20. Zokaei N, Sillence A, Kienast A, Drew D, Plant O, Slavkova E, et al. Different patterns of short-term memory deficit in Alzheimer's disease, Parkinson's disease and subjective cognitive impairment. Cortex. 2020;132:41–50. https://doi.org/10.1016/J.CORTEX.2020.06.016

21. Toniolo S, Maio MR, Tabi YA, Slavkova E, Plant O, Saleh Y, et al. A novel visual short-term memory task differentiates MCI and Alzheimer's patients from healthy ageing. Alzheimers Dement. 2020;16(S6):e043006. https://doi.org/10.1002/alz.043006

22. Tabi YA, Maio MR, Attaallah B, Dickson S, Drew D, Idris MI, et al. Vividness of visual imagery questionnaire scores and their relationship to visual short-term memory performance. Cortex. 2022;146:186–99. https://doi.org/10.1016/J.CORTEX.2021.10.011

23. Pavisic IM, Nicholas JM, Pertzov Y, O'Connor A, Liang Y, Collins JD, et al. Visual short-term memory impairments in presymptomatic familial Alzheimer's disease: a longitudinal observational study. Neuropsychologia. 2021;162:108028. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2021.108028

24. Zokaei N, Nour MM, Sillence A, Drew D, Adcock J, Stacey R, et al. Binding deficits in visual short-term memory in patients with temporal lobe lobectomy. Hippocampus. 2019;29(2):63–7. https://doi.org/10.1002/hipo.22998

25. Bays PM, Catalao RFG, Husain M. The precision of visual working memory is set by allocation of a shared resource. J Vis. 2009;9(10):7. https://doi.org/10.1167/9.10.7

26. Tabi Y, Maio MR, Fallon S, Udale R, Dickson S, Idris MI, et al. Impact of processing demands at encoding, maintenance and retrieval in visual working memory. Cognition. 2021;214:104758. https://doi.org/10.1016/j.cognition.2021.104758

27. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–98. https://doi.org/10.1016/0022-3956(75)90026-6

28. Bucks RS, Haworth J. Bristol activities of daily living scale: a critical evaluation. Expert Rev Neurother. 2002;2(5):669–76. https://doi.org/10.1586/14737175.2.5.669

29. Clark CM, Ewbank DC. Performance of the dementia severity rating scale: a caregiver questionnaire for rating severity in Alzheimer disease. Alzheimer Dis Assoc Disord. 1996;10(1):31–9. https://doi.org/10.1097/00002093-199601010-00006

30. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory. Neurology. 1994;44(12):2308. https://doi.org/10.1212/WNL.44.12.2308

31. https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-5l/. Accessed December 19, 2023.

32. Quality of life in Alzheimer's disease: patient and caregiver reports. PsycNET. Accessed December 8, 2023. https://psycnet.apa.org/record/1999-05045-003

33. Magezi D. Linear mixed-effects models for within-participant psychology experiments: an introductory tutorial and free, graphical user interface (LMMgui). Front Psychol. 2015;6:2. https://doi.org/10.3389/fpsyg.2015.00002

34. Klitgaard H, Verdru P. Levetiracetam: the first SV2A ligand for the treatment of epilepsy. Expert Opin Drug Discov. 2007;2(11):1537–45. https://doi.org/10.1517/17460441.2.11.153

35. Sen A, Jette N, Husain M, Sander JW. Epilepsy in older people. Lancet. 2020;395(10225):735–48. https://doi.org/10.1016/S0140-6736(19)33064-8

36. Toniolo S, Romoli M, Sen A. Epilepsy in older persons. Neurol Clin. 2022;40(4):891–905. https://doi.org/10.1016/j.ncl.2022.03.014

37. Schoenberg MR, Rum RS, Osborn KE, Werz MA. A randomized, double-blind, placebo-controlled crossover study of the effects of levetiracetam on cognition, mood, and balance in healthy older adults. Epilepsia. 2017;58(9):1566–74. https://doi.org/10.1111/EPI.13849

38. Lippa CF, Rosso A, Hepler M, Jenssen S, Pillai J, Irwin D. Levetiracetam: a practical option for seizure management in elderly patients with cognitive impairment. Am J Alzheimers Dis Other Dement. 2010;25(2):149–54. https://doi.org/10.1177/1533317508325095

39. Hawkins K, Dean D, Peralson G. Alternative forms of the Rey auditory verbal learning test: a review. Behav Neurol. 2004;15:99–107. https://doi.org/10.1155/2004/940191

40. Vossel K, Ranasinghe KG, Beagle AJ, La A, Pook KA, Castro M, et al. Effect of levetiracetam on cognition in patients with Alzheimer disease with and without epileptiform activity: a randomized clinical trial. JAMA Neurol. 2021;78(11):1345–54. https://doi.org/10.1001/JAMANEUROL.2021.3310

41. Toniolo S, Sen A, Husain M. Modulation of brain hyperexcitability: potential new therapeutic approaches in Alzheimer's disease. Int J Mol Sci. 2020;21:9318. https://doi.org/10.3390/ijms21239318

42. Toniolo S, Zhao S, Scholcz A, Amein B, Ganse-Dumrath A, Heslegrave AJ, et al. Relationship of plasma biomarkers to digital cognitive tests in Alzheimer's disease. Alzheimers Dement. 2024;16:e12590. https://doi.org/10.1002/dad2.12590

SUPPORTING INFORMATION

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