Tramiprosate as a Novel Treatment for Mild-Moderate Alzheimer Disease

A Systematic Review

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ABSTRACT
Alzheimer Disease (AD) is a chronic neurodegenerative disease. Currently, treatment for AD is limited to symptomatic treatment only, which are cholinesterase inhibitor and memantine. Acting as a symptomatic treatment, those drugs don't act on the pathogenesis of AD. Tramiprosate is a small aminosulfate substance which able to decrease the aggregation of amyloid plaque. Currently there are plenty of studies regarding its effectiveness for the treatment of AD, yet reviews regarding this topic are still lacking **t**o analyze the effect of tramiprosate on clinical outcomes of mild to moderate Alzheimer disease (AD) patients. A systematic review was conducted based on PRISMA through PubMed, ScienceDirect, and CENTRAL, searching for randomized controlled trials which analyze tramiprosate's effects on clinical outcomesof mild to moderate AD patients. Studies selected were then assessed for bias risk with CONSORT criteria. The search yielded six RCTs with a total of 6.346 subjects. Tramiprosate intervention is proven to be effective in reducing ADAS-cog and CBR-SB score while decreasing the decline of hippocampus volume significantly. Furthermore, there are another clinical benefit, such as increasing DAD and cognitive function that showed a positive trend. To conclude, tramiprosate showed promising results to be widely implemented as treatment for mild to moderate AD patients.

Keywords: *Alzheimer Disease, Clinical Outcome, Tramiprosate*

1. INTRODUCTION

Alzheimer disease (AD) is the most prevalent form of dementia. AD is a neurodegenerative disease that manifests as a progressive decrease in cognitive and behavioural function, including memory, language, attention, logic, and judgement. The clinical manifestation of AD depends on the stage of the disease. An early sign that is often observed is episodic short-term memory loss, followed by decreased problem-solving ability and executive function. This condition will continue to progress into a decrease in language ability and visuospatial impairment. Neuropsychiatry and extrapyramidal symptoms will usually emerge in moderate disease [1].

Approximately 46 million people suffer from AD across all countries. In Indonesia, data in 2013 showed that ± 1 million of its population suffers from AD and is projected to double the amount in 2030 and will continue to increase until it is predicted to reach 4 million in 2050 [2]. The risk of developing AD is increased along with age. In fact, the risk of developing this disease increases by 40% after the age of 85 and happens more often in women than in men [2].

Pathogenesis of AD is thought to be involving a failure in the folding process of amyloid-β (Aβ) plaque and the aggregation of Tau protein which, in turn, will tangle the neurofibrillary in the brain. Aβ plaque is a protein that fails to fold and accumulates in the extracellular space with its neurotoxic properties and its ability to cause neuronal loss. Tangled neurofibrillary is an insoluble aggregate consisted of hyperphosphorylated Tau protein. Although the exact relation between the Aβ accumulation and the Tau protein entanglement is still being researched, the current understanding was there is, in fact, an observed

relation between both of them with neuronal and synaptic loss in the cortical region of the brain, which causes a memory loss and cognitive degradation [3] [4].

Currently, there is no definitive treatment for AD. Hence, the current treatment guideline is only to alleviate the symptoms experienced by the patients. The Food and Drug Administration (FDA) has approved two drugs that treat specifically AD symptoms. Those are cholinesterase inhibitors (tacrine, donepezil, rivastigmine, and galantamine) and memantine. The prescription of those drugs depends on the stage of AD. Cholinesterase inhibitor works by decreasing acetylcholine's enzymatic degradation, increasing the acetylcholine level in neuron cells. This drug cannot stop or delay neuronal loss; therefore, its benefit is diminishing along with the progression of neuronal loss because of the lack of acetylcholine production [5] [1].

On the other hand, memantine is used in moderate to severe AD. It works by regulating the glutamate activity, a substance that involves in cognitive and memory function of the brain [5]. The use of cholinesterase inhibitor and memantine does not stop or delay the neurodegenerative process, which is the basic pathogenesis of AD. Hence, this treatment acts as palliative care rather than a curative or disease-modifying treatment [1].

Tramiprosate is a small aminosulfate substance that binds Lys16, Lys28, and Asp23 in Aβ plaque. This bond will stabilize the Aβ monomer, which, in turn, decrease the aggregation of amyloid oligomer and fibrillary plaque. Tramiprosate possess an anti-inflammatory effect, and its molecule also binds to γ-aminobutyric acid (GABA), which acts as a functional agonist [6].

Preclinical studies showed that tramiprosate can decrease the production and deposition of amyloid plaque in murine model. Treatment with tramiprosate caused a significant decrease in soluble and deposited amyloid and also acted on the metabolism and clearance of Aβ. Overall, preclinical studies of tramiprosate showed a neuroprotective mechanism involving GABAnergic and non-GABAnergic pathways [6].

Most Alzheimer-related study uses two main outcomes: The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) and The Clinical Dementia Rating-Sum of Boxes (CDR-SB). ADAS-cog is a cognitive assessment with a range of 0-70 where a higher score is interpreted as higher cognitive dysfunction. Meanwhile, CDR-SB is a clinical scoring system used to assess cognitive dysfunction and functional ability [7]. Another outcome is hippocampus volume related to the pathology of many diseases and a potential marker for intervention given to treat AD. The decrease of hippocampus volume is related to the decrease of cognitive impairment of a patient [8]. Currently, a study regarding the use of tramiprosate to treat AD has undergone a phase III trial. Hence, a need for systematic review regarding the current research progress of the use of tramiprosate as a treatment for AD emerges to act as a foundation for future research and an evaluation for past research.

2. METHOD

2.1. Search Strategy

This systematic review of clinical trials is conducted based on the PRISMA statement. We explored PubMed, ScienceDirect, Cochrane Controlled Register of Trials (CENTRAL), and Wiley databases up to June 3rd 2021, using the following keywords or terms: "Tramiprosate OR 3 APS OR Homotaurine) AND (Alzheimer OR Alzheimer Disease)".

2.2 Inclusion and Exclusion Criteria

Studies were screened according to the inclusion criteria as follows: 1) studies of the effect of tramiprosate on Alzheimer disease patients with extractable outcomes, 2) randomized controlled trial (RCT) study design, and 3) the primary outcome of the study is ADAS-cog score and/or CDR-SB score and/or hippocampus volume. Afterwards, exclusion criteria were also set: 1) irretrievable full-text articles, and 2) inappropriate study design, intervention, or outcome. Details of the study search strategy are shown in Figure 1.

2.3 Data Extraction and Risk of Bias Assessment

Subsequently, we extracted data from our selected articles, including author and year of publication, sample characteristic and size, intervention regiment, primary outcome of ADAS-cog and CDR-SB score, hippocampus volume, and other related outcomes. Articles were also assessed in terms of quality by using CONSORT's criteria (Consolidated Standards of Reporting Trials). The checklist consists of 25 criteria, each score for one point, with a maximum of 25 points. Quality assessment was done collaboratively by all reviewers until consensus was reached.

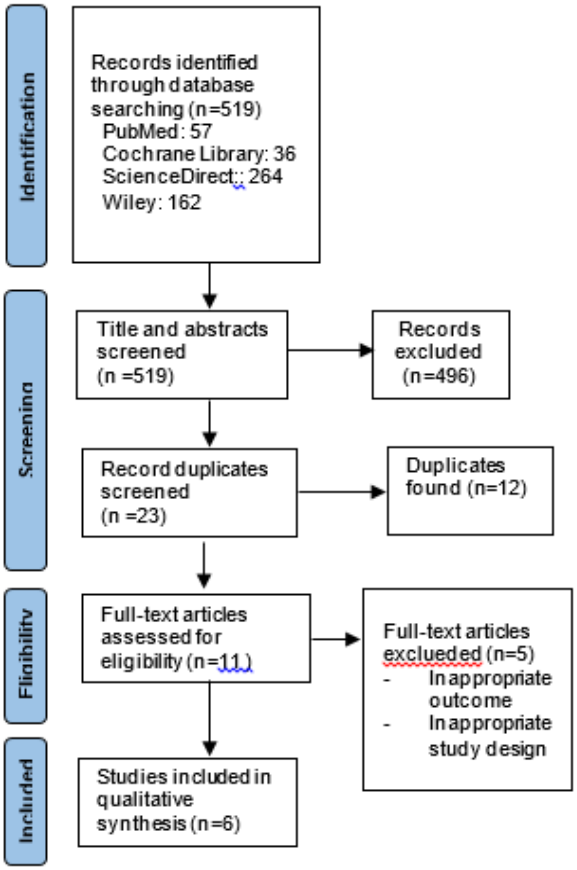

Figure 1 Diagram flow of literature search strategy for this systematic review

3. RESULTS

3.1 Study Selection

The initial search yielded 519 studies from all databases. Among them, 496 were excluded after screening the titles and abstracts. In addition, 12 of them were duplicates hence being excluded. After that, five more studies were being excluded because those studies' outcome was not relevant to this review. In the end, six clinical trials were included for qualitative analysis, all of which were randomized controlled trials (RCT).

3.2 Study Characteristics and Outcomes

The main characteristic of included studies in this systematic review is shown in Table 1. A total of 6.346 patients, mostly elderly, were recruited in this study, comprising studies published between 2002 and 2019. All trials are RCTs, most of which were conducted in North America and Europe. Primary outcomes were ADAS-cog score, CDR-SB score, and hippocampus volume, while the secondary outcome was another related outcome.

In terms of risk assessment, out of all included studies, the lowest calculated CONSORT score was 19.50/25.00 (range: 19.50-21.50). The score means that more than two-thirds of the criteria were fulfilled (>16.67/25.00), which indicates that all the included studies were low at risk of bias and had relatively good qualities.

4. DISCUSSION

4.1 The Effect of Tramiprosate on ADAS-Cog Score

All the included studies measure ADAS-cog as an outcome of the intervention except a study conducted by Roland et al. Across all included studies, the greatest decrease in ADAS-cog is reported by Aisen, PS et al. in 2006 with the intervention of 150mg of tramiprosate [9]. The reported mean change of ADAS-cog in that particular group is -7,5 (SE 1,0; $p<0,05$) after 20 months of follow up [9]. A similar result is also reported by Abushakra et al. in 2016, which, interestingly, divide his results based on apolipoprotein E4 (APOE4) alleles [13]. APOE4 is the most important risk factor for AD. In APOE4 homozygote group, 150mg of tramiprosate group showed a significant decrease of ADAS-cog score (-3,47; SE: 1,27; p=0,0066) in 65 weeks and also in 78 weeks (-2,6; SE: 1,28; p=0,043). A further study by Abushakra et al. in 2017 showed a more significant decrease of ADAS-cog score with 150mg of tramiprosate in mild AD patients (MMSE 20-26) compared to the moderate group (MMSE 16-19) [10]. In week 78, the change from baseline in ADAS-cog score is found to be -5,66 (SE: 1,46; p=0,0001), and the benefit percentage of 150mg tramiprosate to placebo is as much as 125% [10].

The decrease in ADAS-cog score showed an increasing trend in the overall treatment (p=0,084) in a study conducted by Gauthier et al. in 2009 [11]. That particular study found that the mean change of ADAS-cog score after 18 months of follow up is -7,77 (SE: 3,67; p=0,035) in the 150mg group compared to the placebo and after 12 months of follow up is -2,26 (p=0,041) [11].

Only two studies showed a significant decrease with the dose of 100mg. Those are studies conducted by Abushakra et al. in 2017 and Aisen, P S et al. in 2010 [10,12]. In week 78, the mild AD group (MMSE 20-26) showed a decrease of ADAS-cog score by 2,49 (SE: 1,49; p=0,0956) [10]. While Aisen et al. study found the change of ADAS-cog score of -2,0 (p=0,09) after 52 weeks of treatment [9]. Other studies did not show a significant decrease with the dose of 100mg. Among all studies, we found that the tramiprosate intervention is starting to give an observable effect in ADAS-cog score after 26 weeks of treatment. However, overall, the intervention with 150mg of tramiprosate showed an optimal improvement after 52 weeks of treatment.

Table 1. Study Characteristics and Outcomes

Author	Sample Characteristics (n)	Intervention	Primary Outcome (p-value)			Other Outcome (p-value)
			ADAS-cog score	CDR-SB score	Hippocampus Volume	
Abushkara, S et al. 2017	Alzheimer patient with MMSE score 16-26 (n=2025)	Tramiprosate 100mg and 150mg for 78 weeks	100mg = -1.83 (SE=1.22; p=0.13) ; 150mg = -3.55 (SE=1.26; p=0.005)	100mg= -0.18(SE=0.41 ; p=0.67) ; 150mg= -0.81 (SE=0.42; p=0.05)	-	The dose of 150mg increases mean DAD score by 11.39 in 78 weeks (SE=4.03; p=0,006)
Aisen, P S et al. 2010	Alzheimer patient with MMSE score 16-26 ; age >50 (n=1052)	Tramiprosate 100mg and 150mg for 78 weeks	Week 78 =[Control= -6.2; 100mg= -5.4 (p=0,174) ; 150mg= -6.3 (p=0.873)]; Week 52= [Control= -3.1; 100mg= -2.0 (p=0.09); 150mg= -2.3 (p=0.1)]	Week 78 =[Control= -3.0; 100mg= -2.7 (p=0,232) ; 150mg= -3.0 (p=0.915)]; Week 52= [Control= -2.0; 100mg= -1.8 (p=0.335); 150mg= -1.7 (p=0.136)]	Control= -202; 100mg= -210; 150mg= -260 (p=0.035)	-
Aisen, P S et al. 2007	Alzheimer patient with MMSE score 13-25 ; age>50	Tramiprosate 50mg, 100mg, and 150mg for 12 weeks	Week 80= -7.5 (SE=1.9)	Week 80= -2.5 (SE=0.6)	-	-
Abushkara, S et al.2016	Mild-moderate alzheimer patient (n=2025)	Tramiprosate 100mg and 150mg for 78 weeks	Week 65 100 mg [CBL non-carrier = 0.63 (p=0.50) ; heterozygote= -0.80 (p=0.30); homozygote= -1.99 (p=0.11)] Week 78 100 mg [CBL non-carrier= 0.60 (p=0.53); heterozygote= -0.55 (p=0.49); homozygote =-1.22 (p=0.33)] Week 65 150 mg [CBL non-carrier = 1,69 (p=0.071), heterozygote=-0.28 (p=0.72); homozygote = -3.47 (p=0.0066)] Week 78 150 mg [CBL non-carrier= 2.07 (p=0.031); heterozygote= 0.75 (p=0.34); homozygote= -2.60 (p=0.043)]	Week 65 100 mg [CBL non-carrier = 0.24 (p=0.44) ; heterozygote= -0.73 (p=0.0067); homozygote= 0.19 (p=0.64)] Week 78 100 mg [CBL non-carrier=0.32 (p=0.32); heterozygote= -0.73 (p=0.0.0078); homozygote =0.25 (p=0.55] Week 65 150 mg [CBL non-carrier = 0.71 (p=0.024), heterozygote=-0.49 (p=0.065); homozygote = -0.79 (p=0.063)] Week 78 150 mg [CBL non-carrier= 1.15 (p=0.0003); heterozygote= -0.53 (p=0.051); homozygote= -0.54 (p=0.21)]	-	-

4.2 The Effect of Tramiprosate on CDR-SB Score

All of the included studies measured CDR-SB as the main outcome of the intervention given, except the study published by Roland, E et al [14]. All the included studies showed a positive trend in decreasing the CDR-SB score in the dose of 150mg and with the duration of mostly 78 weeks. Across all the included studies, the highest decrease was reported by Aisen, P S, et al. in 2006 using tramiprosate 150mg with the duration of 3 months [9]. The study showed a mean decrease of 2.5 points (p<0,05) in CDR-SB score after 20 months of follow up on 58 Alzheimer patients with an MMSE score of 13-25 [9]. A similar result is also reported by a bigger study conducted by him (Aisen, P S, et al.) in 2010 involving 1052 Alzheimer patients aged >50 with an MMSE score of 16-26 [12]. The aforementioned study reported a 3.0 decrease in CDR-SB score after 78 weeks of treatment with tramiprosate 150mg, though with a very high p-value (p=0,915). Nevertheless, the same study found that in 52 weeks of treatment with 150mg of tramiprosate, there is a better p-value in the decrease CDR-SB score with 1,7 points decreased (p=0,136). A bigger study conducted by Abushakra S et al. in 2017 involving 2025 Alzheimer patients with an MMSE score of 16-26 [10]. Abushakra, S et al. reported

0,81 points (p=0,05) decreased CDR-SB score after 78 weeks of treatment with tramiprosate 150mg [10]. One interesting study conducted by Abushakra et al. in 2016 analyzed further the association of the clinical benefits of tramiprosate in AD with APOE4 alleles. That particular study found that patients with homozygote APOE4 genotype showed the greatest decrease of CDR-SB score (-0.8; SE: 0,42; p=0,063) after 65 weeks of being given 150mg of tramiprosate treatment regimen [13]. Interestingly, this study found a similar decrease of CDR-SB score in the heterozygote group after 100mg of tramiprosate treatment regiment in both 65 and 78 weeks follow up (-0,73; SE: 0,27; p=0,0067). Using 100mg of the dose does not really show a significant decrease in CDR-SB score across all included studies. These findings are consistent with the conclusion of many preclinical studies that showed a dose-dependent characteristic of tramiprosate in reducing the level of amyloid-β in cerebrospinal fluid.

The duration of 65-80 weeks of treatment showed overall positive trends in decreasing CDR-SB score significantly across all studies. Furthermore, the greatest decrease is observed at the end of all included studies (78-80 weeks after treatment). Although, we cannot conclude whether this duration is the peak of clinical benefit of tramiprosate treatment yet because no studies showed a significant decrease in benefit after the intervention. On the other side, all results from the included studies showed a constant increase in clinical benefit over time. Hence, we have not discovered the point of diminishing return from this review, indicating a need for further study with a longer duration to observe whether the clinical benefit will last or stay at all after a longer duration.

4.3 The Effect of Tramiprosate on Hippocampus Volume

A study conducted by Gauthier S et al. in 2009 showed a lower decrease of hippocampus volume in the intervention group compared to the control group [11]. The control group showed a decrease of 419,3 mm3 (p<0,001), while the intervention group with 100mg of tramiprosate showed a significantly less decrease of 135,1 mm3 (p=0,021). The intervention group with 150mg of tramiprosate is showed an even less decrease than both of those groups (79,5 mm3) yet has a very high p-value (p=0,55). Although a similar dose-response relation was found on both hippocampus volume and ADAS-cog score, the overall psychometric and hippocampus volume changes do not correlate significantly. Several reasons behind this may be because psychometric analysis and the vMRI of the hippocampus volume do not directly represent the same disease progression, a different subject may have showed the same global score, but the pattern of change within ADAS-cog or CRD-SB score might be different. Therefore, vMRI can demonstrate a disease-modifying effect, but in further study, a domain-specific neuropsychology test should be involved to acquire a more significant result [11]. Aisen reports a similar result, P S et al. in 2010, which showed that 150mg of tramiprosate (p=0,009) significantly lower the decrease of hippocampus volume in comparison to 100mg of tramiprosate (p=0,035) and especially to the control group (0,098) [12]. Another study also reported a similar effect and concluded that the change in hippocampus volume only showed an intergroup trend that showed a balance in the brain's structural integrity before and after the intervention. The result helps confirms the validity of the randomization process in a study.

4.4 Other Related Outcomes

A study conducted by Abushakra S et al. in 2017 showed a positive trend on Disability Assessment for Dementia (DAD) score in 150mg group with a mean of 11,39 points increased in 78 weeks after treatment (p=0,006) [10]. Meanwhile, a study conducted by Aisen, P S et al. in 2006 showed a significant improvement in MMSE score in 6 months all the way to 20 months while in 3 months it was not significant. This result is thought to be related to the mechanism of tramiprosate action, which does not give any improvement in a short term. The findings support the hypothesized mechanism of tramiprosate, which inhibits fibrillogenesis and the deposition of plaque, therefore delaying neuronal loss in the long term [9].

5. CONCLUSION

Tramiprosate showed promising results to be widely implemented as a treatment for mild to moderate AD patients. It is proven to be effective in reducing ADAS-cog, and CBR-SB score significantly. Furthermore, there are other clinical benefits, such as increasing DAD and cognitive function, showing a positive trend. Although, we cannot conclude whether the duration observed by all included studies is the peak clinical benefit of tramiprosate treatment yet because no studies showed a significant decrease in benefit after the intervention. Hence, we have not discovered the point of diminishing return from this review, indicating a need for further study with a longer duration to observe whether the clinical benefit will last or will it stay at all after a longer duration of treatment.

AUTHORS' CONTRIBUTIONS

A.D conceptualized the idea for the project. AD and CW designed the methodology. A.D, P.D, and V.V performed the literature searching, study screening, quality assessment, data abstraction, and manuscript drafting. C.W verified the analytical methods and

results. A.D and C.W reviewed and edited the manuscript for final submission. All authors have approved the final manuscript for publication.

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