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META-ANALYSIS

The Dose and Duration-dependent Association between Melatonin Treatment and Overall Cognition in Alzheimer's Dementia: A Network Meta-Analysis of Randomized Placebo-Controlled Trials

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Abstract: ***Background*:** While Alzheimer's dementia (AD) has a prevalence as high as 3-32% and is associated with cognitive dysfunction and the risk of institutionalization, no efficacious and acceptable treatments can modify the course of cognitive decline in AD. Potential benefits of exogenous melatonin for cognition have been divergent across trials.

***Objective*:** The current network meta-analysis (NMA) was conducted under the frequentist model to evaluate the potential beneficial effects of exogenous melatonin supplementation on overall cognitive function in participants with AD in comparison to other FDA-approved medications (donepezil, galantamine, rivastigmine, memantine, and Namzaric).

***Methods*:** The primary outcome was the changes in the cognitive function [measured by mini-mental state examination (MMSE)] after treatment in patients with Alzheimer's dementia. The secondary outcomes were changes in the quality of life, behavioral disturbance, and acceptability (i.e., drop-out due to any reason and rate of any adverse event reported).

***Results*:** The current NMA of 50 randomized placebo-controlled trials (RCTs) revealed the medium-term low-dose melatonin to be associated with the highest post-treatment MMSE (mean difference = 1.48 in MMSE score, 95% confidence intervals [95% CIs] = 0.51 to 2.46) and quality of life (standardized mean difference = -0.64, 95% CIs = -1.13 to -0.15) among all of the investigated medications in the participants with AD. Finally, all of the investigated exogenous melatonin supplements were associated with similar acceptability as was the placebo.

***Conclusion*:** The current NMA provides evidence for the potential benefits of exogenous melatonin supplementation, especially medium-term low-dose melatonin, in participants with AD.

***Trial Registration*:** The current study complies with the Institutional Review Board of the Tri-Service General Hospital (TSGHIRB: B-109-29) and had been registered in PROSPERO (CRD42020193088).

Keywords: Alzheimer's dementia, quality of life, cognition, network meta-analysis, dementia, melatonin, circadian rhythm, psychiatry.

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1. INTRODUCTION

Alzheimer's dementia is a highly prevalent disease that increases with age, with a prevalence rate of 3% in those aged 65-74, 17% in those aged 75-84, and 32% in those over 85 [1]. Cognitive dysfunction in Alzheimer's dementia patients is frequently accompanied by behavioral disturbances, depressive mood, and impaired quality of life [2], which increase caregivers' burden and the risk of institutionalization [3-5]. To date, several pharmacologic treatments, such as cholinesterase inhibitors, targeting cognitive dysfunction in Alzheimer's dementia, have been proposed but with unsatisfying results and adverse effects [6]. Developing an effective and tolerable pharmacologic treatment to alleviate cognitive dysfunction in patients with Alzheimer's dementia is an urgent need in clinical practice [6].

Melatonin, which is endogenously secreted from the pineal gland and plays an important role in modulating circadian rhythms [7], has attracted clinicians' attention to the management of Alzheimer's dementia [3, 8, 9]. The disturbance of circadian pacemakers in the hypothalamic suprachiasmatic nucleus (SCN) contributes to cognitive decline in patients with Alzheimer's dementia [10, 11]. Insufficient secretion of melatonin, which is frequently found in patients with Alzheimer's dementia [12-14], is associated with circadian dysfunction [15].

Prior randomized controlled trials (RCTs) attempted to demonstrate the potential benefits of restoring circadian rhythm through exogenous melatonin supplementation on cognition in patients with Alzheimer's dementia. For example, previous RCTs using low dose (2 mg to 2.9 mg) exogenous melatonin supplementation demonstrated significant improvements in cognitive function in patients with Alzheimer's dementia compared to placebos [16, 17]. Furthermore, long-term melatonin use could ameliorate cognitive decline along with aging in patients with Alzheimer's dementia [3]. However, another RCT with short-term high-dose melatonin (10 mg) did not provide significant results in cognitive outcomes [18]. In addition, traditional meta-analyses, by pooling all of the different dosages and treatment durations of exogenous melatonin supplementation into one group, revealed insignificant benefits of exogenous melatonin on cognition in patients with dementia [19-23]. Although, in 2021, the traditional meta-analysis by Sumsuzzman *et al*. [24] demonstrated that the melatonin significantly improved mini-mental status examination (MMSE) score in the mild stage of Alzheimer's dementia, some methodological concerns should be addressed. First, that meta-analysis pooled all different dosages and treatment durations of melatonin into one group to calculate the effect size. Second, that previous meta-analysis merged all different diagnoses into one group (*i.e*., Alzheimer's dementia and mild cognitive impairment). Third, that previous meta-analysis did not make further comparison with other pharmacologic treatments for cognitive function. Therefore, the dose and duration associated efficacy of exogeneous melatonin supplement in patients with Alzheimer's dementia still remains unclear.

Previous studies show that exogenous melatonin supplementation exerts different effects depending on the dosage. Specifically, a low dose is generally thought to have a "high physiological" and "low pharmacological" effect, whereas a high dose is considered to have a "high pharmacological" effect [25-28]. Furthermore, different treatment durations of exogeneous melatonin supplementation exert different effects on cognitive function in patients with Alzheimer's dementia [3]. Therefore, it is more appropriate to consider different dosages and treatment durations of exogenous melatonin as different groups in clinical practice. NMA of existing RCTs enables the estimation of the comparative effectiveness and the understanding of the relative merits of multiple interventions, as well as maximizing statistical power, which cannot be achieved with traditional pairwise meta-analyses [29, 30]. Considering these issues, we conducted an NMA of the published RCTs by estimating the relative effectiveness and acceptability of different dosages and treatment durations of exogeneous melatonin supplementation to elucidate the potential role of melatonin in ameliorating cognitive decline in patients with Alzheimer's dementia.

2. MATERIALS AND METHODS

2.1. General Study Guidelines

The current NMA followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [31] (Supplement Table **S1**) and the AMSTAR 2 appraisal tool [32]. The current study complies with the Institutional Review Board of the Tri-Service General Hospital (TSGHIRB: B-109-29) and had been registered in PROSPERO (CRD42020193088).

2.2. Search Strategy and Selection Criteria

In the current NMA, our search strategy consisted of two stages. In the first stage, we conducted a systematic review using ClinicalKey, Cochrane CENTRAL, Embase, ProQuest, PubMed, ScienceDirect, and Web of Science databases from inception to June 18th, 2020, and finally, the search was updated in August 29th, 2021. In addition, to search for unpublished studies, we also made a search on the platform of ClinicalTrials.gov (Supplement Table **S2**). In the second stage, to include evidence about the efficacy/safety of the FDA-approved oral forms of agents used for episodic migraine management, we conducted an extra search to find RCTs of donepezil, galantamine, rivastigmine, memantine, and Namzaric for the management of Alzheimer's dementia. No language restriction was used. Additionally, manual searches were performed for potentially eligible articles selected from the reference lists of review articles, clinical guidelines, and pairwise meta-analyses [8, 9, 19-24, 33-44].

2.3. Inclusion and Exclusion Criteria

The PICO (population, intervention, comparison, outcome) setting of the current meta-analysis included: (1) P: patients with a diagnosis of Alzheimer's dementia; (2) I: exogenous melatonin supplement (in the part of the extra-search stage for dementia pharmacologic surveillance, the "I" would be the active pharmacologic intervention to alleviate cognitive decline); (3) C: placebo-control; and (4) O: the change in cognitive function. To reduce the heterogeneity, we only included RCTs recruiting patients with Alzheimer's dementia but not mild cognitive impairment. Also, to reduce the potential bias of the placebo effect, we only included published double-blind placebo-controlled RCTs. The inclu-

sion criteria applied in the current NMA included (1) RCTs conducted on patients with Alzheimer's dementia, (2) formally published, (3) trials investigating the efficacy of melatonergic agents, donepezil, galantamine, rivastigmine, memantine, or Namzaric on outcomes of interest, and (4) trials recruiting participants with Alzheimer's dementia only. Therefore, those RCTs consisting of mild cognitive impairment were not included.

The exclusion criteria were those studies (1) not a clinical trial, (2) not an RCT, (3) not reporting the target outcomes, or (4) not related to melatonergic agents, donepezil, galantamine, rivastigmine, memantine, or Namzaric. In cases of duplicated data usage (different articles based on the same sample sources), we included only the article with the largest sample source.

2.4. Data Extraction

Two authors (P.T. Tseng and B.Y. Zeng) independently screened the studies and extracted the relevant information from the manuscripts. In cases of discrepancy, the corresponding author (Y.W. Chen) was consulted. If data were missing from published reports, the corresponding authors or co-authors were contacted to obtain the additional data. We followed a priori-defined unpublished protocol (available upon reasonable request to the corresponding author) and flowcharts used in previous NMAs [28, 45-55].

2.5. Node Definition

Because exogenous melatonin supplementation exerts a different physiological effect according to the dosage (a low melatonin dosage is generally thought to have a "high physiological" and "low pharmacological" effect, whereas a high dose is considered to have a "high pharmacological" effect with a sleep-promoting effect) [25-28], we categorized the melatonin supplementation into "low-dosage," "medium-dosage," and "high-dosage" groups but did not merge all of the melatonin supplementations into one group (Supplement Table **3**). Also, because the different dosages of individual dementia-managing medication exert different efficacy on cognition in Alzheimer's dementia [41], we subgrouped the individual dementia-managing medications according to their dosages. The detailed subgrouping of individual regimens is depicted in Supplement Table **S3** based on the dosage subgroup basis by Dou *et al*. [41]. Further, in a previous report [56], the different efficacy of dementia-managing medications in cognition has been found in different stratifications of treatment durations. Therefore, we categorized the treatment arms according to different treatment durations defined by the previous report, that is, "short term (less than 6 months)," "medium term (at least 6 months but less than 1 year)," "long term (at least one year but less than 2 years)," and "extremely long term (at least 2 years)" [56].

2.6. Outcomes

2.6.1. Primary Outcomes

The primary outcome was changes in cognitive function measured by the MMSE after treatment in patients with Alzheimer's dementia. We used the MMSE as our primary outcome measure for the reasons outlined as follows. (1) The MMSE scores had approximately linear relationships with the quality of life scores (association between Assessment of Quality of Life scale and MMSE scores: $r = 0.30$, $p < 0.0001$) [57]. (2) The MMSE has been widely used and approved to serve as a surrogate for other time-consuming methods of staging dementia, such as the Clinical Dementia Rating (CDR) [58]. (3) The initial MMSE score was significant for determining the time to clinically meaningful decline during longitudinal follow-up [59]. Similarly, the MMSE total score can serve as an index of disease progression and sequence of cognitive decline in patients with Alzheimer's dementia [60]. (4) The MMSE was suitable to evaluate patients with Alzheimer's dementia in a wide range of severity; conversely, the Alzheimer's Disease Assessment Scale-cognition subscale (ADAS-cog) was only suitable for patients with MMSE scores of at least 14 in accordance with the results of previous research [61]. If any of the potentially eligible RCTs did not provide MMSE measurements, we extracted the other secondary outcome data in our NMA, such as changes in quality of life, changes in behavioral disturbances, and acceptability data.

2.6.2. Secondary Outcomes

Secondary outcomes were the changes in quality of life and behavioral disturbances in patients with Alzheimer's dementia. The acceptability was calculated using the dropout rate and rate of any adverse events reported by the principals of intention-to-treat analyses. Specifically, the dropout rate was defined as the percentage of patients dropping out for any reason before study completion.

2.7. Cochrane Risk-of-bias Tool and GRADE Ratings

Two independent authors (P.T. Tseng and Y.W. Chen) evaluated the risk of bias (interrater reliability, 0.85) for each domain described in the Cochrane risk-of-bias tool [62]. We evaluated the certainty of the evidence, including transitivity, precision, and coherence, according to the GRADE framework and previous network meta-analysis by *Cipriani et al.* [63, 64].

2.8. Statistical Analysis

For continuous variables, we estimated the effect size (ES) using the standardized mean difference (StMD) with 95% confidence intervals (CIs). To provide more clinically relevant information to clinicians, we calculated the ES of primary outcomes (MMSE) using the mean difference (MD) with 95% CIs. From the view of clinical practice, the difference between StMD and MD was the clinical meaning. To be specific, from StMD, the clinicians could only know whether there is a statistical significance or not. However, they could not know to what extent this difference is. On the contrary, the MD could tell the clinicians both "whether statistical significance or not" and "to what extent this difference is". For the categorical variables, we used the odds ratio (OR) and 95% CI (the acceptability) and applied a 0.5-zero-cell correction during the meta-analysis. However, if zeroes were present in both the intervention and control arms of one study, we did not apply this correction procedure because of the risk of increasing the bias; instead, these studies were excluded from our analysis [65, 66]. We used the frequentist model of NMA to compare the ES of studies with similar interventions. All of the comparisons were conducted using a two-tailed *t*-test, and $p < 0.05$ was considered statistically significant. Heterogeneity among the included studies was

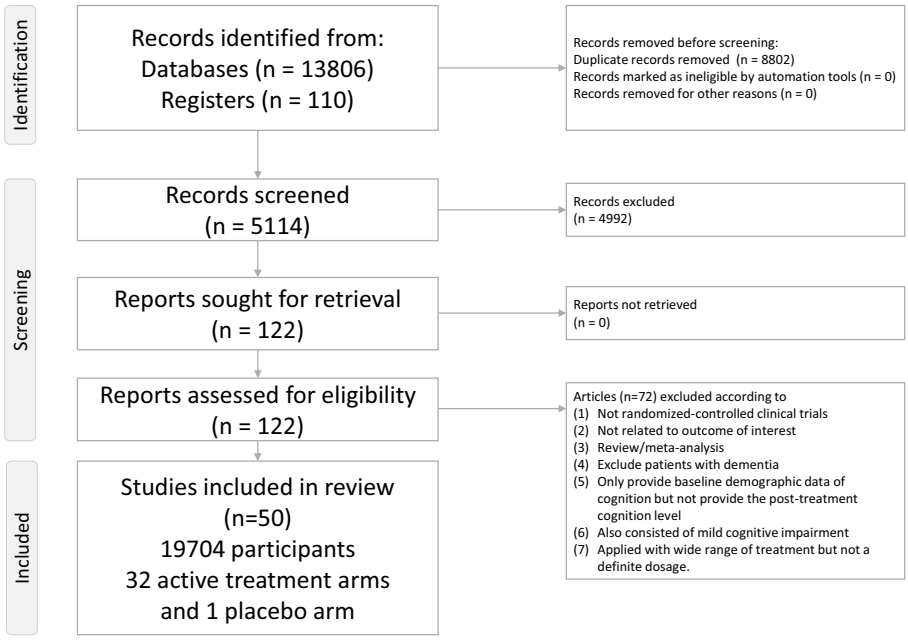

Fig. (1). Flowchart of the current network meta-analysis. Figure **1** depicts the entire flowchart of the current network meta-analysis.

evaluated using the tau value, which was the estimated standard deviation of the effect across the included studies.

We used mixed comparison with generalized linear models to make direct and indirect comparisons [67]. Specifically, indirect comparisons were conducted using transitivity, in which the differences between treatments A and B could be calculated from the comparisons of treatments A *versus* C and treatments C versus B. To compare multiple treatment arms, we combined the direct and indirect evidence from the included studies [68]. STATA version 16.0 (StataCorp Statistics/Data Analysis, StataCorp LLC, College Station, TX, USA) was used in our NMA with the *mvmeta* command [69]. The restricted maximum likelihood method was used to evaluate the between-study variances [70].

To provide additional information for clinical applications, we calculated the relative ranking probabilities of the treatment effects of all of the treatments for the target outcomes. In brief, the surface under the cumulative ranking curve (SUCRA) indicated the percentage of the mean rank of each treatment relative to an imaginary intervention that was the best without uncertainty [71]. When the area under the curve was smaller, the treatment deserved a higher rank of benefit on the cognition in participants with Alzheimer's dementia.

We evaluated the potential inconsistencies between the direct and indirect evidence within the network using the loop-specific approach and identified local inconsistencies via the node-splitting method. The design-by-treatment model was used to evaluate global inconsistencies across the entire NMA [72]. We used comparison-adjusted funnel plots and Egger's regression to evaluate the potentially small study effects in the order of efficacy of individual treatments [73]. Because of the potentially different placebo effects on primary outcomes (cognition measured by the MMSE) in different treatment durations [3], we assessed the effectiveness of the different durations of placebo therapy as additional proof of transitivity in primary outcomes following the rationale and statistical procedure in previous NMA studies [74, 75]. In brief, we computed and compared the difference in the changes in cognition by "short-term," "medium-term," "long-term," and "extremely long-term" duration of placebo therapy using Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ, USA). In situations with significantly different placebo effects among different treatment durations, we arranged further analyses to focus on RCTs according to subgroups with different treatment durations. In addition, to exclude potential confounding effects by concomitant prescriptive medications with effects on cognition, we arranged a subgroup analysis focusing on RCTs that excluded prescriptive medications with effects on cognition.

3. RESULTS

A total of 122 articles were considered in the full-text review (Fig. **1**), of which 68 were excluded for some reasons (Supplement Table **S4**) [8, 9, 19-24, 33-44, 76-127]. Ultimately, 50 articles were included (Supplement Table **S5**) [15-18, 128-173]. Fig. (**2**) depicts the entire geometric distribution of the treatment arms.

3.1. Characteristics of the Included Studies

A total of 19,704 participants were included. The mean age of the participants was 75.1 years (range 65.2 to 85.7 years old), and the mean female proportion was 63.6% (range 0.0% to 85.0%). The mean treatment duration was 34.8 weeks (range 4 to 208 weeks). The baseline characteristics of the included participants are summarized in Supplement Table **S5**.

3.2. Primary Outcome: Changes in Cognition (Measured by the MMSE)

The NMA revealed the medium-term low-dose melatonin (MLT), short-term high-dose donepezil (SHD), medium-term extremely high-dose donepezil (MED), medium-term

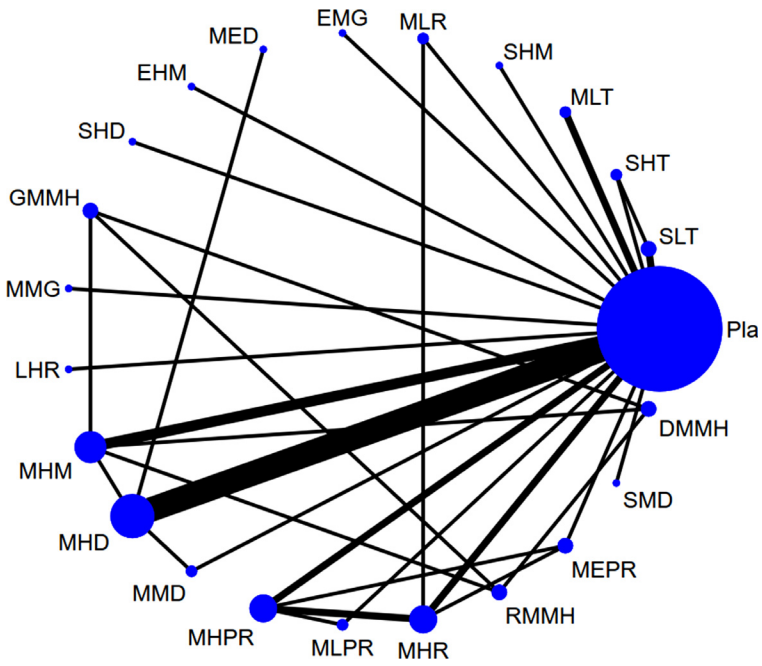

Fig. (2). The network structure of changes in cognitive function. Figure **2** depicts the overall network structure of the current network meta-analysis of changes in cognitive function. The lines between nodes represent direct comparisons in various trials, and the size of each circle is proportional to the size of the population involved in each specific treatment. The thickness of the lines is proportional to the number of trials connected to the network. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

medium-dose donepezil (MMD), medium-term high-dose donepezil (MHD), long-term high-dose rivastigmine (LHR), extremely long-term medium-dose galantamine (EMG), medium-term extremely high-dose rivastigmine patches (MEPR), medium-term high-dose rivastigmine patches (MHPR), and medium-term high-dose rivastigmine (MHR) to be significantly associated with higher post-treatment MMSE than placebos in the participants with Alzheimer's dementia (Table **1**, Fig. **2**, and Fig. **3**). According to the SUCRA, MLT was associated with the highest post-treatment MMSE, followed by MED and SHD (Supplement Table **S6A**).

3.2.1. Transitivity Assumption Test

Because there was only one RCT in the "long-term" duration group in the transitivity assumption test, we did not include the "long-term" duration group in this transitivity assumption test. In brief, there was a significant difference found between the "short-term," "medium-term," and "extremely long-term" durations of placebo therapy ($p < 0.001$, Supplement Fig. **S3**). Furthermore, this significance occurred in the comparison of the "short-term" *vs.* "extremely long-term" groups and "medium-term" *vs.* "extremely long-term" groups. Furthermore, we detected a significant decline in cognition (measured with MMSE) in the extremely long-term placebo therapy group.

3.2.2. Subgroup Analysis

Because there were insufficient RCTs in the "short-term" and "extremely long-term" subgroups ($k = 5$ and 2, respectively), we only arranged further subgroup analyses focusing on RCTs with "medium-term" treatment durations. In brief, the subgroup NMA revealed MLT, MED, MMD, MHD, MEPR, MHPR, and MHR to be associated with a significantly higher post-treatment MMSE than placebos in the participants with Alzheimer's dementia (Supplement Table **S7A**, Supplement Fig. **S1A**, and Supplement Fig. **S2A**). According to the SUCRA, MLT was associated with the highest post-treatment MMSE, followed by MED (Supplement Table **6B**). Further, we arranged subgroup analyses focusing on RCTs that excluded prescriptive medications with effects on cognition. In brief, the subgroup NMA revealed SHD, MLT, MMD, MHD, LHR, MEPR, MHPR, and MHR to be associated with a significantly higher post-treatment MMSE than placebos in the participants with Alzheimer's dementia (Supplement Table **S7B**, Supplement Fig. **S1B**, and Supplement Fig. **S2B**). According to the SUCRA, SHD was associated with the highest post-treatment MMSE, followed by medium-term high-dose memantine plus low-dose galantamine (GMMH) and MLT (Supplement Table **S6C**).

3.3. Secondary Outcome: Changes in Quality of Life

The NMA revealed only MLT, medium-term high-dose memantine plus high-dose donepezil (DMMH), and MHD to be significantly associated with better post-treatment quality of life than placebos in the participants with Alzheimer's dementia (Supplement Table **S7C**, Supplement Fig. **S1C**, and Supplement Fig. **2C**). According to the SUCRA, MLT was associated with the highest post-treatment quality of life (Supplement Table **S6D**).

3.4. Secondary Outcome: Changes in Behavioral Disturbances

The NMA revealed only short-term high-dose memantine (SHM) to be associated with significantly higher improvements in behavioral disturbances than placebos in the participants with Alzheimer's dementia (Supplement Table **S7D**, Supplement Fig. **S1D**, and Supplement Fig. **S2D**). According

Table 1. League table of the improvement in cognition (measured by MMSE).

MLT	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	***1.48 (0.54,2.43)**	-	-	-
0.14 (-1.10,1.37)	MED	-	-	-	0.30 (-0.32,0.92)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
-0.02 (-1.72,1.68)	-0.15 (-1.74,1.43)	SHD	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	***1.50 (0.15,2.85)**	-	-	-
0.16 (-1.68,2.01)	0.03 (-1.71,1.76)	0.18 (-1.92,2.28)	GMMH	-	-	-	-	0.41 (-1.07,1.89)	0.45 (-0.85,1.75)	-	-	-	-	0.82 (-0.58,2.22)	-	-	-	-	-	-	-	-
0.08 (-2.21,2.38)	-0.05 (-2.27,2.16)	0.10 (-2.40,2.60)	-0.08 (-2.68,2.53)	SHM	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.40 (-0.65,3.45)	-	-	-
0.44 (-0.58,1.45)	0.30 (-0.41,1.01)	0.45 (-0.97,1.87)	0.27 (-1.31,1.86)	0.35 (-1.74,2.45)	MHD	0.15 (-0.65,0.95)	-	-	-	-	-	-	-	-0.37 (-1.94,1.20)	-	-	-	-	***1.08 (0.83,1.34)**	-	-	-
0.43 (-0.81,1.66)	0.29 (-0.75,1.33)	0.44 (-1.15,2.03)	0.26 (-1.48,2.00)	0.34 (-1.87,2.56)	-0.01 (-0.77,0.75)	MMD	-	-	-	-	-	-	-	-	-	-	-	-	***1.21 (0.42,2.00)**	-	-	-
0.48 (-0.58,1.55)	0.35 (-0.53,1.22)	0.50 (-0.96,1.96)	0.32 (-1.31,1.95)	0.40 (-1.72,2.52)	0.05 (-0.47,0.56)	0.06 (-0.82,0.93)	LHR	-	-	-	-	-	-	-	-	-	-	-	***1.00 (0.72,1.28)**	-	-	-
0.57 (-1.41,2.56)	0.44 (-1.45,2.32)	0.59 (-1.63,2.81)	0.41 (-1.11,1.93)	0.49 (-2.22,3.19)	0.14 (-1.61,1.89)	0.15 (-1.74,2.04)	0.09 (-1.70,1.87)	RMMH	0.04 (-1.45,1.53)	-	-	-	-	0.41 (-1.17,1.99)	-	-	-	-	-	-	-	-
0.61 (-1.24,2.47)	0.48 (-1.27,2.22)	0.63 (-1.48,2.73)	0.45 (-0.89,1.79)	0.53 (-2.08,3.14)	0.18 (-1.42,1.77)	0.19 (-1.56,1.94)	0.13 (-1.51,1.77)	0.04 (-1.49,1.57)	DMMH	-	-	-	-	0.37 (-1.78,1.04)	-	-	-	-	-	-	-	-
0.75 (-0.35,1.85)	0.61 (-0.30,1.53)	0.77 (-0.72,2.25)	0.59 (-1.06,2.24)	0.67 (-1.47,2.81)	0.31 (-0.27,0.90)	0.32 (-0.59,1.24)	0.27 (-0.40,0.94)	0.18 (-1.63,1.98)	0.14 (-1.52,1.80)	EMG	-	-	-	-	-	-	-	-	***0.73 (0.34,1.13)**	-	-	-
0.77 (-0.29,1.82)	0.63 (-0.23,1.49)	0.78 (-0.67,2.23)	0.60 (-1.02,2.22)	0.68 (-1.43,2.80)	0.33 (-0.17,0.83)	0.34 (-0.52,1.20)	0.28 (-0.31,0.87)	0.19 (-1.58,1.97)	0.15 (-1.48,1.78)	0.02 (-0.64,0.67)	MHPR	0.20 (-0.34,0.74)	0.21 (-0.18,0.59)	-	-	-	0.30 (-0.23,0.83)	-	0.69 (-0.09,1.48)	-	-	-

(Table 1) contd….

0.76 (-0.37,1.89)	0.62 (-0.33,1.58)	0.77 (-0.73,2.28)	0.60 (-1.07,2.27)	0.67 (-1.48,2.83)	0.32 (-0.32,0.97)	0.33 (-0.62,1.29)	0.27 (-0.44,0.99)	0.19 (-1.64,2.01)	0.15 (-1.53,1.83)	0.01 (-0.76,0.78)	-0.01 (-0.57,0.56)	MEPR	0.10 (-0.43,0.63)	-	-	-	-	-	***0.90 (0.35,1.45)**	-	-	-
0.82 (-0.25,1.88)	0.68 (-0.20,1.56)	0.83 (-0.62,2.29)	0.66 (-0.97,2.28)	0.73 (-1.39,2.86)	0.38 (-0.14,0.90)	0.39 (-0.49,1.27)	0.33 (-0.28,0.95)	0.25 (-1.54,2.03)	0.21 (-1.43,1.84)	0.07 (-0.60,0.74)	0.05 (-0.36,0.46)	0.06 (-0.51,0.63)	MHR	-	-	-	-	-	***0.83 (0.39,1.26)**	-	***0.94 (0.24,1.64)**	-
0.98 (-0.18,2.14)	0.85 (-0.13,1.82)	1.00 (-0.53,2.53)	0.82 (-0.62,2.26)	0.90 (-1.27,3.07)	0.55 (-0.13,1.22)	0.56 (-0.43,1.54)	0.50 (-0.26,1.26)	0.41 (-1.20,2.02)	0.37 (-1.08,1.82)	0.23 (-0.58,1.04)	0.22 (-0.53,0.96)	0.22 (-0.63,1.08)	0.16 (-0.60,0.93)	MHM	-	-	-	-	0.33 (-0.31,0.97)	-	-	-
1.35 (-0.04,2.74)	1.21 (-0.04,2.46)	1.36 (-0.35,3.08)	1.19 (-0.67,3.04)	1.26 (-1.04,3.57)	0.91 (-0.13,1.95)	0.92 (-0.33,2.18)	0.86 (-0.22,1.95)	0.78 (-1.22,2.77)	0.74 (-1.13,2.60)	0.60 (-0.52,1.72)	0.58 (-0.49,1.65)	0.59 (-0.56,1.74)	0.53 (-0.55,1.61)	0.37 (-0.81,1.54)	SLT	-	-	-	0.13 (-0.83,1.08)	-	-	0.53 (-0.67,1.73)
1.37 (-0.00,2.75)	***1.24 (0.00,2.47)**	1.39 (-0.31,3.09)	1.21 (-0.64,3.06)	1.29 (-1.00,3.58)	0.94 (-0.08,1.95)	0.95 (-0.29,2.18)	0.89 (-0.17,1.95)	0.80 (-1.19,2.79)	0.76 (-1.09,2.62)	0.62 (-0.48,1.72)	0.61 (-0.45,1.66)	0.62 (-0.51,1.74)	0.56 (-0.51,1.62)	0.39 (-0.77,1.55)	0.03 (-1.37,1.42)	EHM	-	-	0.11 (-0.81,1.03)	-	-	-
***1.28 (0.15,2.41)**	***1.14 (0.18,2.10)**	1.30 (-0.21,2.80)	1.12 (-0.56,2.79)	1.20 (-0.96,3.35)	***0.84 (0.19,1.49)**	0.85 (-0.10,1.81)	***0.80 (0.07,1.52)**	0.71 (-1.12,2.53)	0.67 (-1.01,2.35)	0.53 (-0.24,1.30)	0.51 (-0.07,1.09)	0.52 (-0.24,1.28)	0.46 (-0.20,1.12)	0.30 (-0.56,1.15)	-0.07 (-1.22,1.08)	-0.09 (-1.23,1.04)	MLPR	-	0.00 (-0.52,0.52)	-	-	-
1.58 (-0.61,3.78)	1.45 (-0.67,3.56)	1.60 (-0.81,4.01)	1.42 (-1.10,3.94)	1.50 (-1.36,4.36)	1.15 (-0.84,3.14)	1.16 (-0.95,3.27)	1.10 (-0.92,3.12)	1.01 (-1.61,3.63)	0.97 (-1.55,3.50)	0.83 (-1.20,2.87)	0.82 (-1.19,2.83)	0.83 (-1.23,2.88)	0.77 (-1.25,2.78)	0.60 (-1.47,2.67)	0.24 (-1.97,2.44)	0.21 (-1.99,2.41)	0.30 (-1.75,2.36)	SMD	-0.10 (-2.04,1.84)	-	-	-
***1.48 (0.51,2.46)**	***1.35 (0.59,2.11)**	***1.50 (0.11,2.89)**	1.32 (-0.25,2.89)	1.40 (-0.68,3.48)	***1.05 (0.76,1.33)**	***1.06 (0.30,1.82)**	***1.00 (0.57,1.43)**	0.91 (-0.82,2.64)	0.87 (-0.71,2.45)	***0.73 (0.22,1.25)**	***0.72 (0.31,1.12)**	***0.73 (0.15,1.30)**	***0.67 (0.23,1.10)**	0.50 (-0.13,1.13)	0.14 (-0.86,1.13)	0.11 (-0.86,1.08)	0.20 (-0.37,0.78)	-0.10 (-2.07,1.87)	Pla	0.70 (-1.67,3.07)	0.06 (-0.66,0.78)	0.54 (-0.65,1.73)
2.18 (-0.40,4.77)	2.05 (-0.46,4.56)	2.20 (-0.57,4.97)	2.02 (-0.84,4.88)	2.10 (-1.07,5.27)	1.75 (-0.66,4.16)	1.76 (-0.75,4.27)	1.70 (-0.73,4.13)	1.61 (-1.34,4.57)	1.57 (-1.30,4.44)	1.43 (-1.01,3.88)	1.42 (-1.01,3.84)	1.43 (-1.04,3.89)	1.37 (-1.07,3.80)	1.20 (-1.27,3.68)	0.84 (-1.76,3.43)	0.81 (-1.77,3.39)	0.90 (-1.56,3.37)	0.60 (-2.50,3.70)	0.70 (-1.69,3.09)	MMG	-	-
***1.65 (0.45,2.86)**	***1.52 (0.48,2.56)**	***1.67 (0.11,3.23)**	1.49 (-0.23,3.21)	1.57 (-0.62,3.77)	***1.22 (0.46,1.98)**	***1.23 (0.19,2.27)**	***1.17 (0.34,2.00)**	1.08 (-0.79,2.95)	1.04 (-0.69,2.77)	***0.90 (0.03,1.78)**	***0.89 (0.14,1.64)**	***0.90 (0.04,1.75)**	***0.84 (0.14,1.54)**	0.67 (-0.27,1.62)	0.31 (-0.91,1.53)	0.28 (-0.92,1.48)	0.38 (-0.51,1.26)	0.07 (-2.02,2.16)	0.17 (-0.53,0.88)	-0.53 (-3.02,1.97)	MLR	-
***1.95 (0.40,3.51)**	***1.81 (0.38,3.25)**	***1.97 (0.12,3.81)**	1.79 (-0.19,3.77)	1.87 (-0.54,4.27)	***1.51 (0.27,2.76)**	***1.53 (0.10,2.96)**	***1.47 (0.18,2.75)**	1.38 (-0.73,3.49)	1.34 (-0.65,3.33)	1.20 (-0.11,2.52)	1.19 (-0.09,2.46)	1.19 (-0.15,2.53)	1.13 (-0.15,2.42)	0.97 (-0.40,2.33)	0.60 (-0.61,1.82)	0.58 (-0.97,2.13)	0.67 (-0.67,2.01)	0.37 (-1.94,2.68)	0.47 (-0.74,1.68)	-0.23 (-2.91,2.45)	0.30 (-1.10,1.70)	SHT

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimated effect sizes for the outcome of improvement of cognition in patients with tinnitus. Interventions are reported in order of mean ranking of cognition improvement, and outcomes are expressed as mean difference (MD) (95% confidence intervals). For the pairwise meta-analyses, MD of more than 0 indicates that the treatment specified in the row had more improvement than that specified in the column. For the network meta-analysis (NMA), MD of more than 0 indicates that the treatment specified in the column had more improvement than that specified in the row. Bold results marked with * indicate statistical significance.

to the SUCRA, the SHM was associated with the highest improvement in behavioral disturbances (Supplement Table **S6E**).

3.5. Acceptability Reflected by Dropout Rates

In the NMA, only short-term high-dose rivastigmine (SHR), short-term high-dose galantamine (SHG), MED, medium-term high-dose galantamine (MHG), MHR, MEPR, MHPR, medium-term low-dose rivastigmine patches (MLPR), short-term medium-dose galantamine (SMG), and medium-term medium-dose galantamine (MMG) were associated with significantly higher dropout rates than placebos (Supplement Table **S5C**, Supplement Table **S7E**, Supplement Fig. **S1E**, and Supplement Fig. **S2E**). According to the SUCRA, short-term low-dose melatonin (SLT) was associated with the lowest drop-out rate (Supplement Table **S6F**).

3.6. Acceptability Reflected by the Rate of any Adverse Events Reported

In the NMA, the most investigated treatments, including SHR, SHG, MED, MEPR, MHR, MHG, DMMH, SMG, MHD, MHPR, MLPR, MMG, and EMG were associated with significantly higher rates of any adverse events reported than placebos (Supplement Table **S5C**, Supplement Table **S7F**, Supplement Fig. **S1F**, and Supplement Fig. **S2F**). According to the SUCRA, medium-term low-dose rivastigmine (MLR) was associated with the lowest rate of any adverse events reported (Supplement Table **S6G**).

3.7. Risk of Bias, Publication Bias, Inconsistency Assessment, and GRADE Ratings

We found 74.3% (260/350 items), 23.4% (82/350 items), and 2.3% (8/350 items) of the included studies to have, overall, a low, unclear, and high risk of bias, respectively. Unclear reporting of the allocation procedures and blinding of the participants or research personnel were the most often encountered reasons for the high risk of bias (Fig. **S4A**-**S4B**). Funnel plots of the publication bias (Fig. **S5A**-**S5J**) revealed general symmetry, and the results of Egger's test indicated no significant publication bias among the articles included in the NMA. In general, the NMA did not demonstrate inconsistencies in terms of either local inconsistencies as assessed using the loop-specific approach and node-splitting method or global inconsistencies as determined using the design-by-treatment method (Table **S8**-**S10**). The results of the GRADE evaluation are listed in the appendix. In brief, the overall quality of evidence of the NMA, direct evidence, and indirect evidence was low to medium (Supplement Table **S11**).

4. DISCUSSION

The current work is the first study using the NMA statistics technique to provide a view of the potential benefits of melatonin for Alzheimer's dementia compared to the other FDA-approved dementia-managing medications. In the current NMA, we found medium-term low-dose melatonin (MLT) to be associated with the highest post-treatment MMSE among all of the investigated medications in the participants with Alzheimer's dementia. This finding did not change after focusing on RCTs with medium-term treatment duration. Furthermore, the significantly beneficial effects on cognition of MLT were still found when focusing on RCTs that excluded concomitant medications. MLT was also associated with the highest post-treatment quality of life in the participants with Alzheimer's dementia. All of the investigated exogenous melatonin supplements were associated with similar acceptability with respect to the drop-out rate or rate of any adverse events reported, as was the placebo.

The most important finding of the current NMA was that medium-term low-dose melatonin was associated with the highest post-treatment MMSE in the participants with Alzheimer's dementia. This finding differed from those of previous traditional meta-analyses [19-22]. By pooling the effect sizes of all of the different dosages and treatment durations of exogenous melatonin into one group, prior traditional meta-analyses revealed insignificant benefits of exogenous melatonin on cognition in patients with dementia. As addressed in the previous review article, low- to medium-dose exogenous melatonin affected the phase of sleep-wake rhythms, and high-dose exogenous melatonin showed hypnotic effects on older participants [174]. Similar dose-dependent effects of exogenous melatonin on cognition could also be found in the previous RCTs. Specifically, significant beneficial effects on MMSE were found in patients with dementia receiving medium-dose melatonin supplementation [15-17] but not those receiving high-dose melatonin supplementation [18, 175]. Furthermore, according to the previous RCT [3], low-dose melatonin in medium- to long-term but not short-term use could ameliorate cognitive decline along with the aging process [3]. Therefore, based on the current NMA and previous RCTs [3, 15-18, 175], we hypothesize that the potential beneficial effects of exogenous melatonin on cognition might be restricted to a specific dosage for medium-term use, which might have a therapeutic window of low-dose (less than or equal to 3 mg/day) and medium-term use (at least 6 months but less than 1 year), but not a medium- or high-dose and short-term use.

The rationale of exogenous melatonin supplementation to improve cognitive function in patients with Alzheimer's dementia could be supported by physiologic and pharmacologic evidence. Previous reports [176, 177] demonstrate that the neuron numbers of the suprachiasmatic nucleus (SCN), which mainly modulates the effect of endogenous melatonin, decrease with aging and dementia. In addition, in age-matched controlled trials, serum melatonin levels were significantly lower in patients with dementia, especially Alzheimer's dementia, than those in normal controls [13, 14]. In addition, patients with Alzheimer's dementia have been found to be associated with not only the irregularity of endogenous melatonin in patients with dementia [12], but also with circadian rhythm disorders and sleep-wake rhythm disturbances [178, 179]. Insomnia at night and daytime sleepiness were prevalent and significantly correlated with the MMSE (Pearson's $r = 0.62$, $p < 0.05$) in patients with Alzheimer's dementia [180]. Furthermore, decreased sleep quality could impose adverse impacts on mental function [15] and worsen the progression of Alzheimer's dementia [181-183] by increasing beta-amyloid deposition [184, 185]. Through the evidence from previous traditional meta-analyses, exogenous melatonin supplementation could improve sleep efficiency [22] and increase total sleep time at night but not during the day [21]. Therefore, exogenous

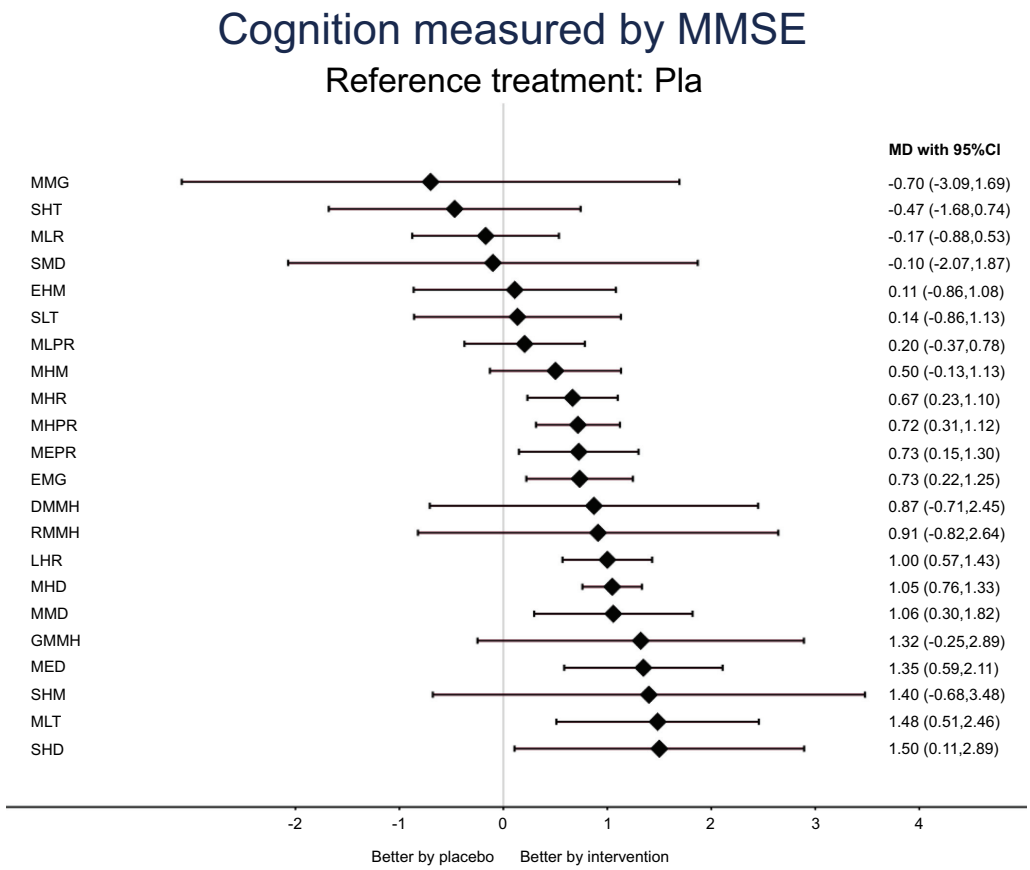

Fig. (3). Forest plot of changes in cognitive function. Figure **3** indicates that, when the effect size is more than zero, the specified treatment is associated with higher improvements in cognitive function in patients with Alzheimer's dementia than placebos in the measurement of MMSE. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

melatonin supplementation, which could restore circadian rhythm [186] and improve sleep quality [22, 27], is a potential choice to alleviate the adverse impact of circadian rhythm disturbance and poor sleep quality on cognitive function in patients with Alzheimer's dementia.

In addition to circadian rhythm restoration and sleep quality improvement, there are three potential mechanisms by which melatonin might be able to alleviate Alzheimer's dementia severity. The first mechanism is the anti-oxidative effect of melatonin supplementation [187]. In a previous research, Alzheimer's dementia was frequently associated with increased oxidative stress, and regimens with antioxidative stress effects might exert potential beneficial effects on cognitive function [188]. The second mechanism is its antagonism effect on beta-amyloid proteins [17]. Melatonin *in vitro* not only inhibits beta-amyloid protein generation, but also arrests the formation of amyloid fibrils by structure-dependent interactions with beta-amyloid proteins [189]. The third mechanism is its inhibitory effect on the hyperphosphorylation of Alzheimer-like tau protein, which might be associated with the progression of Alzheimer's dementia [190].

4.1. Limitations

There are several limitations to be addressed in the current NMA. First, some analyses in this study were limited by underpowered statistics, including heterogeneity in the participants' characteristics (for example, comorbid diseases, different concomitant medications, a wide variety of ages, lack of uniform diagnostic criteria for Alzheimer's dementia, a wide variety of rating scales of secondary outcomes, and trial durations) and the small number of trials for some treatment arms. Second, because of the weak network structure (*i.e.*, the limited number of the direct connections between active interventions), especially that of the secondary outcomes, the results of the current NMA should be interpreted with caution. Third, although we tried to include other kinds of melatonergic regimens (ramelteon and agomelatine) by adding these keywords to our search strategy, we found only RCTs with exogenous melatonin supplementation. Future RCTs focusing on different melatonergic regimens in patients with Alzheimer's dementia are warranted to assess their efficacy. Fourth, as addressed in the discussion, as the treatment duration increased, the different effects on cognition of dementia-managing medications and placebos were more significant [3]. Nevertheless, the relatively overall short treatment duration among the recruited RCTs (mean duration = 34.8 weeks, range 4 to 208 weeks) limited the application of the results of the current NMA. Fifth, although we tried to arrange a subgroup analysis based on RCTs excluding concomitant prescriptive medications, the potential bias by concomitant prescriptive medications could not be completely eliminated. Finally, although our study was strengthened by comparing different treatments with NMA, the generalization of our results was still highly limited de-

pending on the studies included and the possible comparisons within them. Future studies are warranted to assess the efficacy of melatonergic agents focusing on the optimal dosage and treatment duration for the alleviation of cognitive decline in Alzheimer's dementia in different medical settings. Clinicians should consider specific strategies in specific clinical conditions.

CONCLUSION

The current NMA has provided an overview of the potential effect of exogenous melatonin supplementation, especially medium-term low-dose melatonin, on the amelioration of cognitive decline in patients with Alzheimer's dementia. Specifically, the current NMA found medium-term low-dose melatonin to be associated with the highest post-treatment MMSE and quality of life in participants with Alzheimer's dementia. However, because of the small numbers of included studies, the current NMA provided a potential view to encourage future large-scale and long-term treatment and follow-up duration RCTs to focus on the efficacy of different dosages and treatment durations of exogenous melatonin supplementation on cognitive dysfunction in patients with Alzheimer's dementia.

LIST OF ABBREVIATIONS

CI = Confidence interval

DMMH = Medium-term high dose memantine plus high dose donepezil

EHM = Extreme-long-term high dose memantine

EMG = Extreme-long-term medium dose galantamine

ES = Effect size

GMMH = Medium-term high dose memantine plus low dose galantamine

LHR = Long-term high dose rivastigmine

LLT = Long-term low dose melatonin

MA = Meta-analysis

MD = Mean difference

MED = Medium-term extreme high dose donepezil

MEM = Medium-term extreme high dose memantine

MEPR = Medium-term extreme high dose rivastigmine patch

MHD = Medium-term high dose donepezil

MHG = Medium-term high dose galantamine

MHM = Medium-term high dose memantine

MHPR = Medium-term high dose rivastigmine patch

MHR = Medium-term high dose rivastigmine

MLPR = Medium-term low dose rivastigmine patch

MLR = Medium-term low dose rivastigmine

MLT = Medium-term low dose melatonin

MMD = Medium-term donepezil medium dose

MMG = Medium-term medium dose galantamine

MMSE = Mini-mental status examination

NMA = Network meta-analysis

OR = Odds ratio

Pla = Placebo

PRISMA = Preferred reporting items for systematic reviews and meta-analyses

RCT = Randomized controlled trial

RMMH = Medium-term high dose memantine plus medium dose rivastigmine

SHD = Short-term high dose donepezil

SHG = Short-term high dose galantamine

SHM = Short-term high dose memantine

SHR = Short-term high dose rivastigmine

SHT = Short-term high dose melatonin

SLG = Short-term low dose galantamine

SLT = Short-term low dose melatonin

SMD = Short-term medium dose donepezil

SMG = Short-term medium dose galantamine

SMT = Short-term medium dose melatonin

StMD = Standardized mean difference

SUCRA = Surface under the cumulative ranking curve

AUTHORS' CONTRIBUTIONS

Ping-Tao Tseng, Bing-Yan Zeng, and Yen-Wen Chen, who contributed equally as first authors, took the whole responsibility of literature search, data extraction, and manuscript drafting. Chun-Pai Yang, Kuan-Pin Su, Tien-Yu Chen, Yi-Cheng Wu, Yu-Kang Tu, Pao-Yen Lin, Andre F. Carvalho, Brendon Stubbs, Yutaka J. Matsuoka, Dian-Jeng Li, Chih-Sung Liang, Chih-Wei Hsu, Cheuk-Kwan Sun, Yu-Shian Cheng, and Pin-Yang Yeh contributed to study design, concept formation, and major revision of the manuscript. Yow-Ling Shiue, who contributed as the corresponding author, took the responsibility of the collection of all information from the other co-authors, major revision of the manuscript, and full access to the data.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines were followed for the study.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

PRISMA checklist is available on the publisher's website along with the published article.

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