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Evidence for the Efficacy of Latrepirdine (Dimebon) Treatment for Improvement of Cognitive Function: A Meta-Analysis

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Abstract. Over the last few years, latrepirdine, a démodé antihistamine drug, has been proposed to be useful for treating neurodegenerative disorders such as Alzheimer's and Huntington's diseases, and more recently schizophrenia. The mechanisms and pharmacological targets that are responsible for the beneficial effects on neurodegenerative diseases remain unknown. But it has been proposed that latrepirdine may modulate several targets including voltage-gate Ca^{+2} channels, mitochondrial permeability pore transition, or several neurotransmitter receptors. Herein, we present a meta-analysis of randomized controlled trials to ascertain the efficacy and safety of latrepirdine on cognitive function. By doing a search in electronic databases, we found five clinical trials in which the effect of latrepirdine on cognition function has been studied, and this was evaluated using MMSE, ADAS-cog, ADCS-ADL, and NPI scores. Latrepirdine generally presented a good safety profile; it was well tolerated when given alone or in combination with a variety of other drugs. We observed heterogeneous results between trials; latrepirdine failed to exert a significant beneficial effect although it tended to improve cognitive scores. The only significant benefit that we found was for the NPI score in Alzheimer's disease patients.

Keywords: Alzheimer's disease, clinical trials, cognition function, dimebon, Huntington's disease, schizophrenia

INTRODUCTION

Clinically, neurodegenerative diseases [Alzheimer's disease (AD) and Huntington's disease (HD)] manifest themselves as a gradual decline of cognitive functions such as learning and memory, progressing to dementia [1, 2]. Even though these pathologies were described more than a century ago, there still is no efficient treatment to restore cognitive functions. This lack drives, with relative frequency, the pharmacologist to turn to their established pharmaceutical arsenal, which has the advance that these drugs have a well described safety profile.

An example is latrepirdine (Dimebon®, dimebolin, or 2,3,4,5- Tetrahydro-2, 8-dimethyl-5-(2-6(6-methyl-3- pyridyl)ethyl)-1H-pyrido(4,3-b) indole) (Fig. 1A). Latrepirdine is an orally available non-selective antihistamine receptor, which was withdrawn from the market with the development of more selective antihistaminic compounds. Recent findings demonstrated that latrepirdine improved learning in animals with

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experimental AD [3]. However, the basis for this clinical effect remains unknown. It is being postulated that latrepirdine, besides its originally described anti-histaminic effects, may modulate several other targets including neurotransmitter receptors (e.g., α-adrenergic, serotonin, dopamine, imidazole, glutamate) (Fig. 1B, also see [4]). Among these targets are those mediating deregulation of the intraneuronal calcium concentration ($[Ca^{2+}]_i$), which can be responsible for activation of cell death pathways [5]. Doing so, latrepirdine might modulate anti-apoptotic routes that are involved in the loss of cognitive function and thus might have the potential to exert disease-modifying properties (neuroprotection) [6]. Even more, recently it has been postulated that latrepirdine might have a pro-autophagic role [7–9].

In the last five years, all the clinical relevance of latrepirdine as a potential drug to ameliorate the cognitive impairment has been questioned due to apparent discrepancies between clinical trials [10–13]. However, in a recently published double-blind and placebo-controlled randomized trial to measure the efficacy of latrepirdine in schizophrenic patients, Morozova et al. documented that latrepirdine had a positive impact on most tested parameters of cognitive activity [14].

The statistical technique of meta-analysis, combining the findings from independent studies, has proven to be very useful in the interpretation and aggregation of data in clinical science, and thus may be of great value to help assess the clinical effectiveness of healthcare interventions [15]. At present there is no meta-analysis available in the literature that is focused on the effect of latrepirdine on the cognitive functions of patient with neurodegenerative diseases such as AD or HD. Therefore, the aim of this study is to review the field of latrepirdine and to discuss tolerability, safety, and efficiency of this drug.

MATERIAL AND METHODS

We conducted a search for all randomized controlled trials comparing latrepirdine with placebo or other therapies in patients that are affected by neurodegenerative diseases such as AD or HD. The studies were found by a search in MEDLINE using the terms "dimebon" and "latrepirdine". The same terms were used in the Cochrane Central Register of Controlled trials (CENTRAL) database (up to May 2013). The bibliographic references of the selected articles were also examined to locate other possible publications that were not found in the above-mentioned search. In this way, we collected 127 articles. Of these studies, 103 were rejected for various reasons (Fig. 2). Of the 24 remaining studies, eight were included in our systematic review and five clinical trials were included in the present meta-analysis (Table 1 and Fig. 2). Usefulness of the identified publications describing controlled studies of latrepirdine given in AD and HD was judged independently by two investigators (NC-C, JSGdP), and disagreements were resolved in discussion with a third investigator (JJ). We have contacted the authors of two identified but unpublished (CONNECTION and CONCERT) trials, and these investigators have kindly provided their efficacy results.

We collected data on patient diagnosis, dosage used, duration of treatment and follow-up, inclusion and exclusion criteria, scales used for efficacy, and rate of adverse events. We assessed the quality of the studies using the Jadad score, which considers aspects related to biases, such as randomization, blinding, and reporting of loss to follow-up [16]. This instrument gives a score from 0 (the worst score) to 5 (the best score).

We have used safety and tolerability measures. Safety was assessed by the adverse events described in the trials and the percentage of participants that experienced a serious adverse event as defined in the trials. Tolerability was assessed as the percentage of participants that abandoned the treatment.

The primary efficacy outcome parameter was the change from baseline the end of the treatment in the Mini-Mental State Examination (MMSE) score [17]. The MMSE is a common, validated screening instrument that is used as a general measure of cognitive function (lower score indicate greater impairment).

We included the following as secondary efficacy outcomes:

- Alzheimer's Disease Cooperative Study-activities of daily living (ADCS-ADL) was designed to evaluate functional capacity over a broad range of severities in patients with AD [18]. It has 23 items and the possible scores range from 0 to 78 (with lower scores indicating greater impairment).
- Alzheimer Disease Assessment Scale-cognitive subscale (ADAS-cog) [19] measures cognitive function consisting of eleven items (word recall, naming, commands, constructional praxis, orientation, word recognition, instructions remembering, spoken language ability, word-finding difficulty, and comprehension). Scores range from 0 to 70 with high scores indicating poor cognitive function.

Table 1
Studies included in the review

Trial[Ref]	*n*	Patients	Trial phase	Daily latrepirdine dose	Control	Design	Efficacy measures	Jadad score	Follow-up (days)
Bachurin [3]	14	AD	I	60 mg (20 × 3)	No control	Open label	Hasegawa scale Butakina scale	0	56
Doody [6]	183	AD	II	60 mg (20 × 3)	Placebo	Double blind	ADAS-cog MMSE NPI ADCS-ADL CIBIC-plus	5	182
Tariot [23]	24	AD receiving donezepil	I	Dose titration (2.5 to 20 mg or 10 to 20 mg × 3)	Placebo	Double blind	–	n/a	28
CONNECTION [12]	398	AD	III	60 mg (20 × 3) or 15 mg (5 × 3)	Placebo	Double blind	ADAS-cog CIBIC-plus ADCS_ADL NIP MMSE	n/a	180
Kieburtz [21]	91	HD	II	60 mg (20 × 3)	Placebo	Double blind	UHDRS[6] MMSE ADAS-cog	5	104
CONCERT [11]	662	AD	III	60 mg (20 × 3) or 15 mg (5 × 3)	Placebo	Double blind	ADCS-ADL CIBIC-plus NPI	n/a	365
Morozova [14]	56	Schizophrenic	III	20 mg	Placebo	Double blind	PANSS CDRS AIMS SAS BAS	3	56
HORIZON [13]	403	HD Disease	III	60 mg (20 × 3)	Placebo	Double blind	MMSE NPI ADCS-ADL	4	182

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; ADCS-ADL, Alzheimer's Disease Cooperative Study- Activity of Daily Living; CIBIC-plus, Clinician's Interview-based Impression of Change plus Caregiver Input; UHDRS, Unified Huntington's Disease Rating Scale; PANSS, Positive and Negative Syndrome Scale; CDRS, Calgary Depression Rating Scale; AIMS, Abnormal Involuntary Rating scale; SAS, Simpson-Angus Scale for Extrapyramidal Symptoms; BAS, Barnes Akathisia Scale.

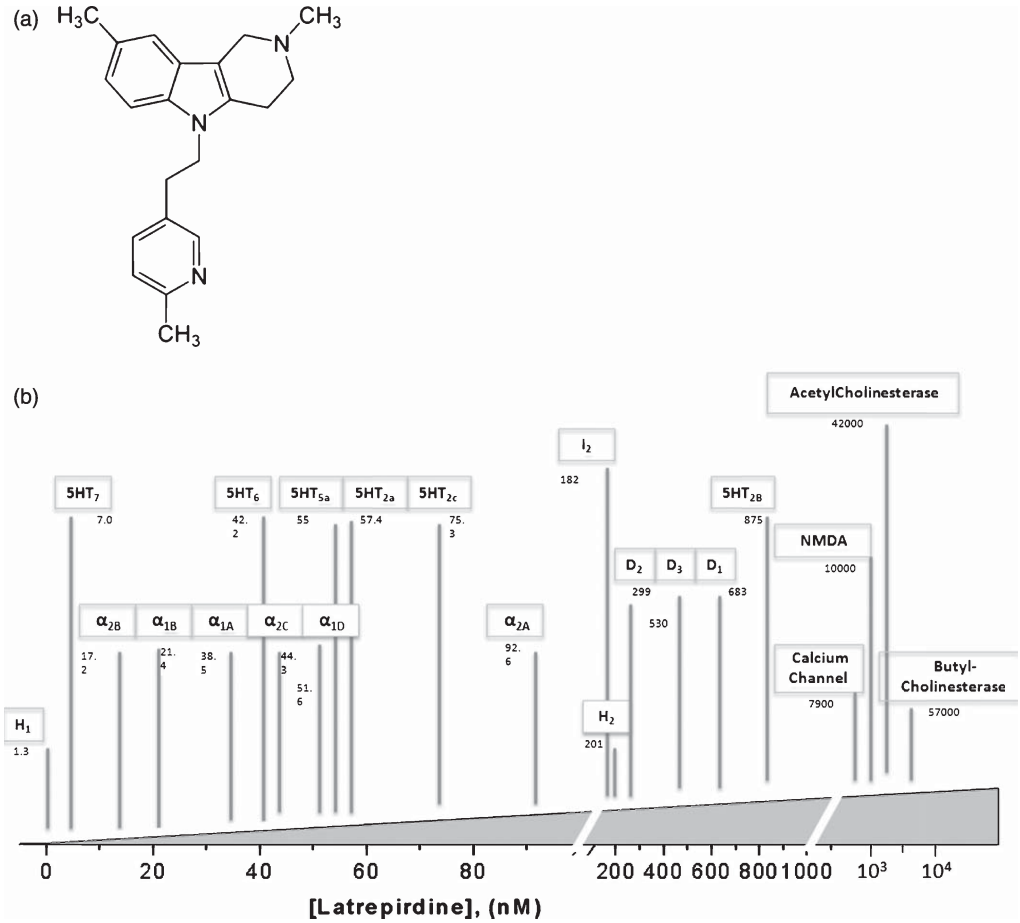

Fig. 1. Latrepirdine. A) Chemical structure. B) Pharmacological targets.

- The Neuropsychiatric Inventory (NPI) was developed to assess psychopathology in dementia patients [20]. It evaluates twelve neuropsychiatric disturbances. The scores range from a minimum of 0 to a maximum of 144. The higher the score, the more severe is the psychopathology.

Statistical analyses were performed to compare latrepirdine with placebo in terms of efficacy, tolerability, and safety wherever such comparison was possible. Differences in tolerability were expressed as a risk ratio with 95% confidence interval (CI). The efficacy measures (MMSE, ADAS-cog, NPI, ADCS-ADL) were expressed as mean differences with the relevant confidence interval (95%CI). We have used a fixed-effect model, using a random effect where heterogeneity between studies was found. Chi^2 of heterogeneity and I^2 inconsistency statistics were used to measure heterogeneity in the study results. In all tests, the level of statistical significance used was $p < 0.05$. Analyses were performed using RevMan version 5.

RESULTS

Electronic database searching yielded a total of 127 potentially eligible articles. Eight papers were included in our review, of which seven papers described clinical trials reporting the effect of latrepirdine on cognition function. Only five trials used some of the selected cognitive efficacy measures and these were included in the quantitative analysis [6, 11–13, 21]. Table 1 summarizes characteristics and Jadad scores of the eight clinical trials with patients suffering from either mild to moderate AD [3, 6, 11, 12, 22, 23], mild to moderate HD [13, 21], or schizophrenia [14].

In none of the reports analyzed was a justification of dose usage found, but we noted that latrepirdine was administered in the range of 5 to 20 mg per day

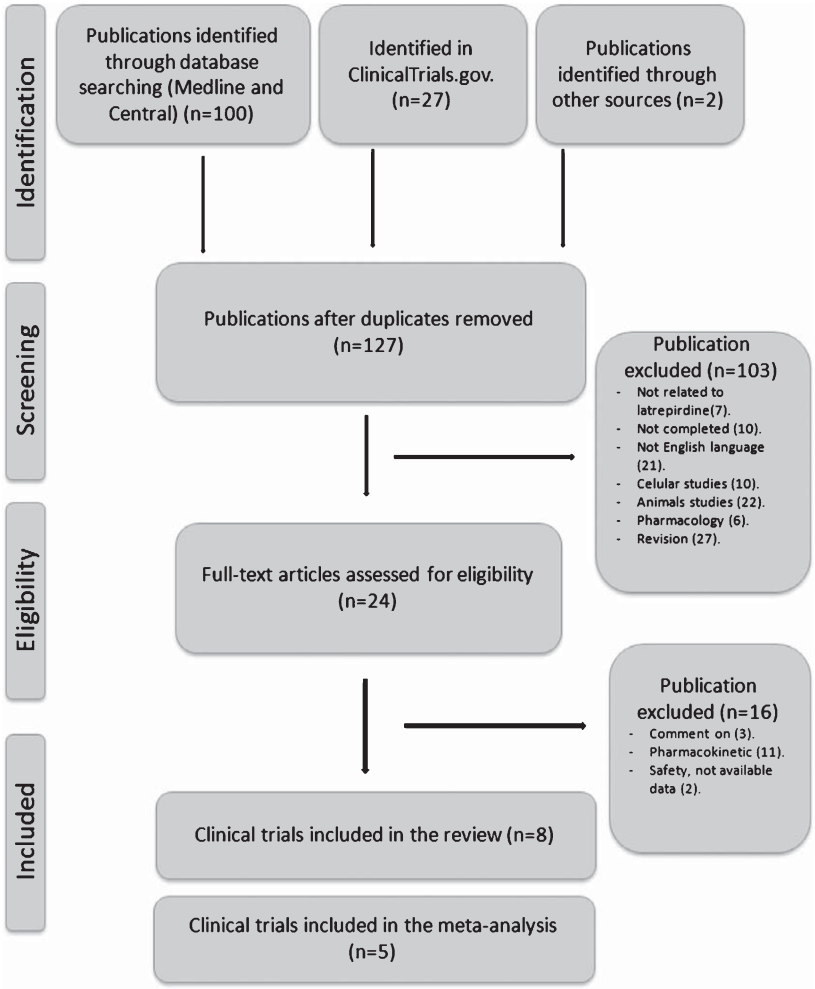

Fig. 2. Flow chart outlining the search strategy and results of the different steps.

(Table 1). In four trials, latrepirdine was administered at 20 mg or 10 mg three times per day for the first 7 days [6, 13], whereas Kieburtz used an initial regimen of 10 mg latrepirdine on day 1 followed by a dosage of 10 mg three times per day for the next six days [21]. In the CONNECTION trial [12], an arm of 5 mg was included to define the effective dose range for latrepirdine treatment.

Latrepirdine: Tolerability and safety

Generally, latrepirdine presented a good safety profile. Table 2 summarizes the adverse events that occurred more frequently. Among them, the most relevant adverse event of latrepirdine as compared to placebo was the occurrence of a dry mouth. This adverse event exceeded 6 % (21/335 versus placebo 3/341, $p < 0.001$). Fatigue was the second most frequent adverse event and was experienced by 3% of the patients (10/335 versus placebo 0/341, $p < 0.004$).

The number of patients that stopped the treatment was similar between latrepirdine and placebo groups (risk ratio 0.73; 95%CI 0.47 to 1.14; $p = 0.16$) [6, 13, 21]. Thus, latrepirdine was well tolerated. Moreover, latrepirdine was also well tolerated when given in combination with various other drugs, including the cholinesterase inhibitor donepezil [23] and warfarin [22].

Latrepirdine: Cognitive function

As primary efficacy outcome we determined the change in the MMSE. Three trials were performed using patients with mild to moderate AD. First, in the Doody trial, latrepirdine improved the MMSE score versus placebo ($p < 0.0001$) in patients with mild to

moderate AD [6]. Second, in the CONNECTION trial, although both groups improved significantly as compared to the baseline status (latrepirdine 0.7; placebo 1.2), no significant difference was found between latrepirdine and placebo ($p = 0.10$) [12]. In the third trial, also no difference between latrepirdine and placebo was observed [11]. On the other hand, two trials were found using HD patients. In the randomized Kieburtz trial, latrepirdine improved the MMSE score as compared to placebo ($p = 0.03$) [21]. Interestingly, a higher difference between latrepirdine and placebo (1.63 points, 95%CI 0.44 to 2.82; $p = 0.008$) was found in the subgroup of participants with a more severe cognitive impairment (MMSE score ≤ 26) [21]. However, no significant differences were observed between different treatment groups in patients with HD in the Horizon trial ($p = 0.39$) [13]. When we analyzed effect of latrepirdine in a disease-independent manner, we detected that, although latrepirdine seems to result in a favorable MMSE score, the differences found were not significant (0.57; IC95% −0.27 to 1.40; $p = 0.18$) (Fig. 3A).

In patients with mild to moderate AD, latrepirdine improved the ADCS-ADL scores at week 26 ($p = 0.002$) [6]. Nevertheless, the CONNECTION and CONCERT trials failed to reproduce this result ($p = 0.61$ and $p = 0.54$) (Fig. 3B). Similar results were found in HD patients treated with latrepirdine ($p = 0.22$) [13].

Four clinical trials registered the changes from baseline of ADAS-cog (Fig. 3C). Contradictory results were found in AD patients. Only in Doody's study, latrepirdine improved this score by 0.2 points versus placebo ($p > 0.0001$) [6]. However, both posterior trials, CONNECTION or CONCERT, showed no significant differences (0.1 and 0.8 points difference, respectively) between latrepirdine-treated patients and patients receiving placebo ($p = 0.86$ and $p = 0.22$) [11, 12]. Consistent with the later studies, no apparent effects of latrepirdine were found on the ADAS-cog ($p = 0.79$) in HD patients [21]. Taken together, we conclude that, although the ADAS-cog score has improved upon latrepirdine treatment as compared to baseline, these differences were not significant (−1.03; 95%CI −2.34 to 0.28; $p = 0.12$) (Fig. 3C).

The mean changes in NPI score showed a significant benefit in AD patients of treatment with latrepirdine as compared to placebo in the Doody trial ($p = 0.006$) [6]. In posterior studies, latrepirdine-treated groups showed a 1.6 point ($p = 0.17$) improvement as compared to placebo in CONNECTION [12], and a 0.7 point ($p = 0.49$) improvement in CONCERT [11]. Taken together all results with AD patients, latrepirdine displayed significant improvement as compared to placebo in the NPI score (−1.83; 95%CI −3.45 to −0.21; $p = 0.03$) (Fig. 3D). However, latrepirdine did not result in a significant difference in this score in patients with HD (difference 0.10; $p = 0.82$) [13].

DISCUSSION

In this study, we have evaluated the effects of treatment with latrepirdine, an old anti-histaminic drug, on the cognitive function in patients with degenerative diseases such as AD and HD. This meta-analysis includes all available data up to June 2013 and reveals that latrepirdine failed to exert a significant beneficial effect although it tended to improve cognitive scores (as measured by MSME, ADCS-ADL, ADAS-cog, and NPI) in AD and HD patients.

To our knowledge, this is the first meta-analysis performed to ascertain the effect of latrepirdine on cognitive function. Even more, by contacting the authors of two unpublished trials, this study has avoided one of the main handicaps of a meta-analysis, which is the fact that they are based only on published data. We detected that the clinical trials using latrepirdine were rather heterogeneous, possibly because they were carried out in different settings. But, by performing a meta-analysis and a systematic revision, we are in situation to evaluate and join data from different clinical trials. Nevertheless, we cannot exclude the existence of other clinical trials with negative studies since these are less likely to be published.

Our results show that latrepirdine only presents a beneficial effect when the NPI scale was used in AD patients. Although this drug also seemed to slightly improve the scores of other scales, it failed to exert a significant beneficial effect. Also, we have to remark that the first clinical trial [6] influenced the above observations as it was the clinical trial with the more positive results in all the scales used and these results have not been confirmed by posterior studies. An important point is also the difference in dynamics of placebo groups in the different trials. In the Doody trial, cognitive scores in the placebo group declined during the study, as is expected in this group of AD patients, while in the CONNECTION and CONCERT trials, no such decline was observed. We do not know if this difference is due to population differences between the trials. Possibly, latrepirdine can prevent further decline in cognition but, due to the results with the placebo group in the CONNECTION

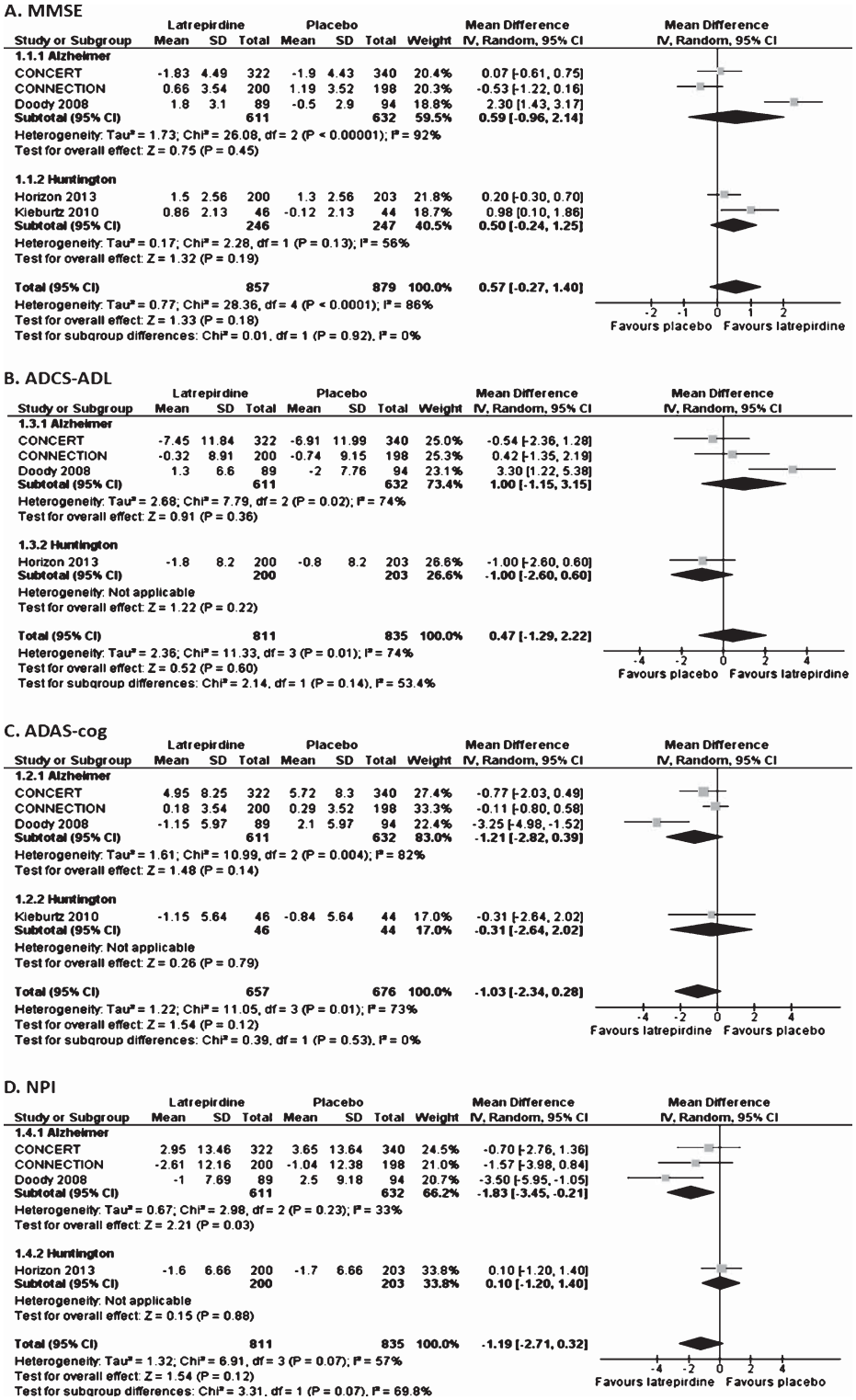

Fig. 3. Comparison of latrepirdine versus placebo in terms of improvement of cognitive function. Efficacy outcome parameter was the change from baseline at the end of the treatment in the Mini-Mental State Examination (MMSE) score (A), Alzheimer's Disease Cooperative Study-activities of daily living (ADCS-ADL) (B), Alzheimer Disease Assessment Scale-cognitive subscale (ADAS-cog) (C), and Neuropsychiatric Inventory (NPI) (D).

and CONCERT trials, it was impossible to ascertain this. Thus, with the available data, we cannot confirm this hypothesis. Moreover, in an AD pre-clinical approximation, latrepirdine failed to modulate the age-related impairment in spatial learning in the Morris water maze, and exerted no effect on the age-related increase in hippocampal expression of several markers [24]. Supporting a lack of effect on cognitive function, latrepirdine fails to afford beneficial effects in HD patients. Indeed, in the ADCS-ADL scale, the placebo group presents a better score than latrepirdine.

Unexpectedly, our systematic review revealed the lack of a single original manuscript describing either the exact mechanism or the specific pharmacological target that could justify the above-proposed effects. Responsible targets for such effects remain unknown. Conceivably, the effect of latrepirdine can be explained by the modulation of several families of receptors (as summarized in Figs. 1 and 2). One of the more relevant pathways proposed is the stabilization of neuronal Ca^{2+} signaling, which has been shown to be perturbed in HD and AD [25]. Latrepirdine inhibits NMDA receptors [26], AMPA receptors [4], voltage-gated Ca^{2+} channels [27], and the mitochondrial permeability transition pore [28]. Consistent with this mechanistic hypothesis, memantine, an FDA-approved drug for AD, acts as an open-channel blocker of the NMDA receptor. However, latrepirdine needs to reach 50 μM concentration levels to achieve neuroprotective effects, which is not likely to be achieved in human trials. In AD trials of latrepirdine, the patients received 20 mg pills [6], which should not lead to concentrations higher than 0.6 μM assuming an ideal absorption and blood brain-barrier brain permeability profile. Thus, most beneficial effects of latrepirdine are likely to be due to its properties as a cognitive enhancer based on its ability to inhibit H1 histamine receptors with IC50 = 3.4 nM [3]. In addition, recent studies from several laboratories pointed to other potential targets of latrepirdine action. These studies described that latrepirdine led to a retardation of pathology progression in animal models, possibly because it depletes the levels of proteinaceous aggregates formed by –amyloid-β peptides, huntingtin, synucleins TDP-43, or tau [7–9, 29–34]. The fact that latrepirdine activates autophagy processes, which are involved in some neurodegenerative diseases, has driven this drug to be considered as a scaffold for discovery of novel anti-neurodegeneration compounds [7–9].

Interestingly, other drugs in the vanguard of the neuroprotector battery modulate a sustenance number of targets. In line with this, new therapeutic approaches for the treatment of neurodegenerative disorders compromise drug candidates that are specifically designed to act on multiple targets. This also seems to be the case for minocycline, a tetracycline antibiotic, which modulates many of the hypothesized pharmacological targets of latrepirdine (for reviews, see [35, 36]). Minocycline prevents neurons against excitotoxic stimuli [37, 38] and induces neuroprotection in AD and HD experimental models [39, 40]. Moreover, several clinical trials have been conducted to examine the effect of this drug on cognitive alteration, including HD, AD, and HIV-associated cognitive impairment [6, 11, 12, 41].

DISCLOSURE STATEMENT

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1848).

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