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Cognitive changes under memantine according to vitamin D status in Alzheimer patients: An exposed/unexposed cohort pilot study

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ABSTRACT

Memantine is a symptomatic treatment that partially prevents cognitive decline in Alzheimer disease (AD). The neuroprotective effects of memantine and vitamin D may potentiate each other, with benefits for cognition. The objective of this exposed/unexposed pilot study was to determine the cognitive changes among AD patients using memantine according to the presence or absence of vitamin D deficiency (VDD). Fifty-eight AD patients followed in a memory clinic during 6 months between 2009 and 2014 (mean ± standard deviation, 82.9 ± 5.0years; 56.9%female) were separated into four groups according to VDD (i.e., serum 25-hydroxyvitamin D ≤ 25 nM) at M0 and M6 (i.e., Group 1: no VDD-M0, no VDD-M6; Group 2: VDD-M0, no VDD-M6; Group 3: no VDD-M0, VDD-M6; Group 4: VDD-M0, VDD-M6). The 6-month cognitive change was examined with the Mini-Mental State Examination (MMSE) score in the 4 groups according to the use of memantine. Age, gender, body mass index, IADL score, GDS score, and use of pchychoactive drugs were measured at baseline. We found that participants using memantine had a lower MMSE score at M0 compared to those without memantine (P = 0.006). After 6 months of follow-up, there was a memantine-related improvement of the MMSE score only in the participants with VDD-M6. This was significant in Group 3 with no VDD-M0 (P = 0.039), but not in Group 4 who already had VDD-M0. Similarly, using memantine was associated with a 6-month improvement of MMSE only in Group 3 in whom VDD appeared during the follow-up (β = 8.8, P = 0.044). In conclusion, the use of memantine was associated with improved cognitive performance after 6 months of treatment in the presence of VDD at M6. Memantine may prevent the cognitive decline that accompanies the onset of VDD, which prompts to give to AD patients a regimen combining both memantine and vitamin D supplements.

1. Introduction

Alzheimer disease (AD) is the most common neurodegenerative dementia, responsible for cognitive decline and loss of autonomy in older adults, with greater risks of institutionalization, hospitalization and death [1]. AD is caused by various pathophysiological mechanisms including amyloid plaques, neurofibrillary tangles, and glutamatergic neurotoxicity [2]. There are no curative drugs available to date, but only symptomatic treatments such as memantine. Memantine is an *N*-methyl-D-aspartate (NDMA) receptor antagonist. It reduces the glutaminergic neurotoxicity and intraneuronal calcium entry during AD, thereby limiting neuronal cell death and subsequent cognitive decline [3]. Memantine is commonly used since more than a decade to prevent declines in cognition, behavior and autonomy among AD patients [4]. However, the effects of memantine are only partial and temporary, and brain decline is postponed but not stopped. Interestingly, it has been suggested that a multidrug regimen combining memantine with another neuroprotective molecule could enhance the efficacy of memantine [5]. For instance, it was reported that the combination of memantine with vitamin D supplements was more effective than memantine alone to prevent cognitive decline among AD patients [6].

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Vitamin D is involved in neurophysiology and neuronal protection [7]. It exerts anti-inflammatory [8] and antioxidant effects [9], vascular protection [10] and calcium regulation in the central nervous system [11]. Consistently, vitamin D deficiency (VDD) is associated with cognitive decline in older adults [12,13], although vitamin D supplementation is associated with cognitive improvements [14,15].

We proposed that the neuroprotective effects of memantine and vitamin D supplements may potentiate each other [5]. However, since there is no dose-dependent relationship between vitamin D supplies and serum vitamin D concentration, health events are generally related primarily to the serum concentration of 25-hydroxyvitamin D (25OHD) rather than to the use of supplements. We thus hypothesized that the cognitive efficacy of memantine may actually depend on patients' serum 25OHD concentration. The aim of this pilot exposed/unexposed study was to determine the cognitive changes of AD patients using memantine according to their circulating vitamin D status.

2. Material and methods

2.1. Participants

Data were retrospectively collected from the patients' database of the Memory Clinic of Angers University Hospital, France. The inclusion criteria were as follows: 1) outpatients aged 65 years and older visiting the Memory Clinic between 2009 and 2014 inclusively; 2) outpatients with at least one follow-up visit after 6 ± 2 months; 3) *de novo* diagnosis of AD with Mini-Mental State Examination (MMSE) score $\leq$26; 4) no prescription of anticholinesterasics (i.e., donepezil, galantamine or rivastigmine) and/or vitamin D supplements; 5) blood test with 25OHD measure at baseline and after 6 months. Fifty-eight outpatients met the inclusion criteria and were included in the analysis (Fig. 1). Their clinical characteristics are summarized in Table 1. Medications were reported by direct inquiry and from the primary care physician's prescription. Diagnostic and Statistical Manual, 4th edition (DSM IV) criteria were used to establish the clinical diagnosis of dementia in the absence of delirium and regardless of the length and stage of dementia [16]. AD was diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) work group [17].

All included participant received a full medical examination at baseline and at the end of the follow-up including interview, physical examination, a standardized geriatric examination, blood test and cognitive tests.

2.2. Use of memantine

Some participants used memantine as part of their routine care. In this case, the date of visit 1 (i.e., inclusion into the study) was that of the first prescription of memantine. A nurse dispended drugs to improve adherence to treatment. Memantine was administered orally at a dose of 20 mg once daily in the morning – titrated in 5 mg increments over 4 weeks. In case of severe renal insufficiency, the dose was 10 mg per day, as recommended in the summary of product characteristics. The choice of the anti-dementia drug (i.e., memantine or anticholinesterasics) was made by the responsible physician based on indications, contra-indications and national guidelines. Using no anti-dementia drug was eventually explained either by the patients' or relatives' refusal, or by contra-indications, or by a delayed introduction of treatment due to the paraclinical investigations required before the prescription of such treatment.

2.3. Between-visit change in global cognitive performance: MMSE score change

The MMSE score [18] was used to assess global cognitive performance during the study and was carried out at baseline (i.e., before the prescription of memantine) and at the follow-up visit after 6 months by a neuropsychologist without knowledge of the treatment used. MMSE is a well-established measure of cognitive function in older adults composed of five sections (orientation, registration, attention–calculation, recall, and language). It shows good test-retest and inter-rater reliability and performs satisfactorily against more detailed measures of cognitive function [18]. Scores range from 30 (normal) to 0 (impaired). The change of MMSE score was used to assess the change in cognitive performance after the introduction of the treatment.

2.4. Serum 25OHD measures

Venous blood was collected at baseline and at M6 from participants to determine the serum 25OHD concentration. Radioimmunassay was used (DiaSorin, IncstarCorp, Stillwater, MN). With this method, there is no interference of lipids, which is often observed in other nonchromatographic assays of 25OHD. The intra- and interassay precisions were respectively 5.2% and 11.3%, (range in normal adults aged 20–60 years, 75–375 nM). As previously described [19], vitamin D deficiency (VDD) was defined as serum 25OHD $\leq$ 25 nM.

2.5. Covariables

Age, gender, body mass index (BMI), IADL score, geriatric depression scale (GDS) score, use of pchychoactive drugs were measured at baseline. A balance scale was used to measured weight and a height gauge to determine the height. The BMI was calculated as weight/height^2 in kg/m^2. Psychoactive drugs (i.e., neuroleptics, benzodiazepine, or andidepressants) were retrieved by screening personal prescription and patients' and relatives' interview. The 4-item Geriatric Depression Scale (GDS) was used to evaluate the mood, with total score between 0 and 4 (worst) [20]. The autonomy was assessed with the 8-item IADL score (Instrumental Activities of Daily Living) [21] with a score ranging between 0 and 8 (best).

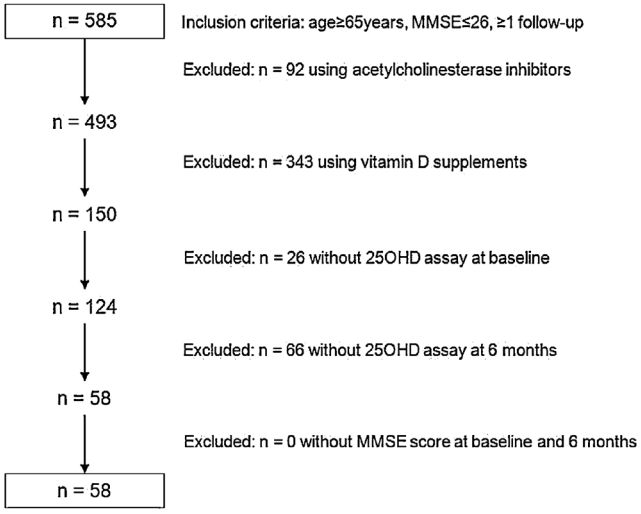

Fig. 1. Flow diagram of the selection of participants.

Table 1
Participants' characteristics according to the use of memantine (n = 58).

Characteristics at M0	Total cohort (n = 58)	Participants using		P-value[a]
		memantine (n = 18)	no memantine (n = 40)	
Age, years	82.9 ± 5.0	83.4 ± 3.7	82.7 ± 5.6	0.814
Female gender, n (%)	33 (56.9)	10 (55.6)	23 (57.5)	0.890
Body mass index, kg/m^2	25.1 ± 4.0	24.8 ± 3.4	25.2 ± 4.3	0.990
MMSE score at M0,/30	19.6 ± 5.0	17.1 ± 4.5	−0.6 ± 3.6	**0.006**
MMSE change between M0-M6[b],/30	−0.2 ± 3.5	0.7 ± 3.0	1.9 ± 1.5	0.217
IADL score,/4	1.9 ± 1.4	1.8 ± 1.3	1.9 ± 1.5	0.817
GDS score,/4	0.9 ± 1.0	0.7 ± 1.0	0.9 ± 1.0	0.496
Use psychoactive drugs, n (%)	37 (63.8)	12 (66.7)	25 (62.5)	0.760
Serum 25OHD concentration, nM	57.9 ± 34.8	57.6 ± 39.7	58.0 ± 32.9	0.680
Vitamin D deficiency[c] at M0, n (%)	15 (25.9)	6 (33.3)	9 (22.5)	0.383
Vitamin D deficiency[c] at M6, n (%)	9 (15.5)	5 (27.8)	4 (10.0)	0.084
Serum calcium concentration, mmol/L	2.31 ± 0.11	2.29 ± 0.09	2.32 ± 0.11	0.572
Serum TSH concentration, mUI/L	1.46 ± 0.98	1.31 ± 0.80	1.52 ± 1.05	0.935

Data presented as mean ± standard deviation when appropriate; 25OHD: 25-hydroxyvitamin D; GDS: Geriatric Depression Scale; IADL: Instrumental Activities of Daily living; M0: month 0; M6: month 6; MMSE: Mini-Mental State Examination; PTH: parathyroid hormone; TSH: thyroïd stimulating hormone.
[a] comparisons based on Mann-Whitney *U* test or Chi-square test, as appropriate.
[b] calculated as: 'MMSE score at M0–MMSE score at M6'.
[c] serum 25OHD ≤ 25 nM; P-value significant (i.e., P < 0.05) indicated in bold.

2.6. Statistical analysis

The participants' characteristics were summarized using means and standard deviations or frequencies and percentages, as appropriate. Firstly, comparisons between the total cohort and the participants actually included in the present analysis were performed with non-parametric Mann-Whitney *U* test or Chi-square test, as appropriate. Secondly, comparisons between participants separated into two groups based on the use of memantine were performed with non-parametric Mann-Whitney *U* test or Chi-square test, as appropriate. Thirdly, comparisons between participants separated into four groups according to the vitamin D status at M0 and M6 (i.e., Group 1: no vitamin D deficiency ≤25 nM at M0 and no vitamin D deficiency at M6; Group 2: vitamin D deficiency at M0 and no vitamin D deficiency at M6; Group 3: no vitamin D deficiency at M0 and vitamin D deficiency at M6; Group 4: vitamin D deficiency at M0 and vitamin D deficiency at M6) were performed using non-parametric Kruskal-Wallis H test or Chi-square test, as appropriate. When applicable, post-hoc analyses were performed using Mann-Whitney *U* test. Fourthly, the change in MMSE score was examined based on the use of memantine according to the four groups of vitamin D status using non-parametric Kruskal-Wallis H test. Fifthly, age-adjusted linear regression models were used to predict the change in MMSE score between M0 and M6 from the use of memantine according to the four groups of vitamin D status. All statistics were performed using SPSS (v.19, IBM corporation, Chicago, IL).

2.7. Ethics

Participants in the study were included after having given their informed consent for research. The study was conducted in accordance with the ethical standards set forth in the declaration of Helsinski (1983). The study protocol was approved by the local Ethical committee.

3. Results

Five hundred heighty-five participants (mean ± standard deviation, 82.9 ± 5.0 years, 56.9% female) met the inclusion criteria. After applying exclusion criteria, 58 participants were finally recruited in the present analysis (Fig. 1). The characteristics of the studied sample (n = 58) were similar at baseline to those of the total cohort (n = 585). In particular, there was no difference in age (P = 0.864), gender (0.360), MMSE score (P = 0.868), IADL score (P = 0.918), GDS score (P = 0.215), use of psychoactive drugs (P = 0.231), serum 25OHD concentration (P = 0.415) and VDD prevalence (P = 0.344). Only the BMI differed between groups (26.4 ± 4.7 versus 25.1 ± 4.0 kg/m^2; P = 0.022).

Table 1 shows the 58 participants' characteristics according to the use of memantine at baseline. Participants using memantine had a lower MMSE score compared to those without memantine (17.1 ± 4.5 versus 20.2 ± 5.2; P = 0.006), but there was not significant difference in the MMSE change between M0 andM6 (respectively, 0.7 ± 3.0 versus −0.6 ± 3.6; P = 0.217). There were also no difference in the prevalence of VDD at M0 (33.3% versus 22.5%; P = 0.383) and M6 (27.8% versus 10.0%; P = 0.084) between the participants who used memantine and those who did not.

Table 2 indicates the characteristics of the participants according to the presence of VDD at M0 and M6. There was no statistical difference between groups, except for the 25OHD concentration. In particular, there was no MMSE difference at baseline (P = 0.549), and no difference in MMSE change between M0–M6 (P = 0.876).

Fig. 2 shows the MMSE change between M0-M6 according to the use of memantine and the presence of VDD at M0 and M6. We found a significant difference only in the participants for whom VDD appeared during the follow-up (i.e., no VDD at M0, but VDD at M6): those who used memantine had a significant improvement of the MMSE score compared to those who did not use memantine (P = 0.039).

Finally, Table 3 reports the results of the age-adjusted linear regression models showing the associations between the use of memantine (independent variable) and the change in MMSE score between M0-M6 (dependent variable) according to the finding of VDD at M0 and M6. The only significant association between memantine and MMSE change was found in the group in whom VDD appeared during the follow-up (β = 8.8, P = 0.044). There were no significant associations in the other groups.

4. Discussion

The main finding of our study is that the use of memantine was associated with improved cognitive performance after 6 months of treatment only in the presence of vitamin D deficiency at M6. This finding was significant among AD patients without vitamin D deficiency at baseline, and there was a nonsignificant tendency among those with vitamin D deficiency at baseline, just as if

Table 2
Characteristics of participants separated into four groups according to vitamin D deficiency (VDD) at M0 and M6 (n = 58).

Characteristics at M0	Participants				P-value[a]						
	Group 1 (n = 39) No VDD-M0 No VDD-M6	Group 2 (n = 10) VDD-M0 No VDD-M6	Group 3 (n = 4) No VDD-M0 VDD-M6	Group 4 (n = 5) VDD-M0 VDD-M6	Over-all	G1 vs G2	G1 vs G3	G1 vs G4	G2 vs G3	G2 vs G4	G3 vs G4
Age, years	82.5 ± 5.5	83.5 ± 3.6	82.8 ± 3.8	84.9 ± 4.9	0.675	–	–	–	–	–	–
Female gender, n (%)	21 (53.8)	4 (40.0)	3 (75.0)	5 (100.0)	0.131	–	–	–	–	–	–
Body mass index, kg/m^2	24.6 ± 4.0	25.6 ± 3.5	25.0 ± 1.3	29.5 ± 5.3	0.167	–	–	–	–	–	–
MMSE score at M0,/30	19.7 ± 5.3	20.2 ± 4.8	16.5 ± 3.9	20.4 ± 3.8	0.549	–	–	–	–	–	–
MMSE change between M0-M6[b],/30	−0.2 ± 3.5	−0.4 ± 2.7	−0.5 ± 4.5	0.4 ± 4.5	0.876	–	–	–	–	–	–
IADL score,/4	2.0 ± 1.5	1.9 ± 1.5	1.7 ± 1.5	1.0 ± 1.0	0.712	–	–	–	–	–	–
GDS score,/4	0.9 ± 1.1	0.9 ± 0.9	1.3 ± 1.5	0.3 ± 0.6	0.760	–	–	–	–	–	–
Use psychoactive drugs, n (%)	25 (64.1)	6 (60.0)	2 (50.0)	4 (80.0)	0.810	–	–	–	–	–	–
Use memantine, n (%)	9 (23.1)	4 (40.0)	3 (75.0)	2 (40.0)	0.149	–	–	–	–	–	–
Serum 25OHD concentration, nM	74.9 ± 28.0	18.1 ± 4.8	47.3 ± 21.8	13.4 ± 2.9	**<0.001**	**<0.001**	**0.049**	**<0.001**	**0.002**	0.055	**0.016**
Serum calcium concentration, mmol/L	2.32 ± 0.12	2.27 ± 0.10	2.31 ± 0.08	2.28 ± 0.03	0.590	–	–	–	–	–	–
Serum TSH concentration, mUI/L	1.39 ± 0.93	1.83 ± 1.22	1.17 ± 0.44	1.43 ± 1.16	0.747	–	–	–	–	–	

Data presented as mean ± standard deviation when appropriate; 25OHD: 25-hydroxyvitamin D; GDS: Geriatric Depression Scale; IADL: Instrumental Activities of Daily living; M0: month 0; M6: month 6; MMSE: Mini-Mental State Examination; PTH: parathyroid hormone; TSH: thyroïd stimulating hormone; VDD: vitamin D deficiency.
[a] comparisons based on Kruskal-Wallis H test, Mann-Whitney *U* test or Chi-square test, as appropriate.
[b] calculated as: 'MMSE score at M0–MMSE score at M6'; P-value significant (i.e., P < 0.05) indicated in bold.

memantine prevented the cognitive impairments that accompanied the onset of vitamin D deficiency. This finding strengthens the need to prevent vitamin D deficiency in AD patients, and prompts to give a regimen combining memantine with vitamin D supplements to AD patients.

To the best of our knowledge, no study has examined yet the cognitive efficacy of memantine according to vitamin D status. Only one experimental study in cultured cortical neurons showed potentiating benefits of the combination of memantine with vitamin D supplements on axonal survival after addition of AD stressors such as Aβ peptide or glutamate [22]. Similarly, one study in moderate-to-severe AD patients reported that those using memantine plus vitamin D supplements for six months had a statistically and clinically relevant cognitive gain of 4 points on the MMSE score, although those treated with memantine or vitamin D supplements separately had a slight cognitive decline [6]. Based on these two previous studies, it was hypothesized that memantine and vitamin D may combine their neuroprotective effects to enhance protection against neuronal and cognitive disorders in AD [5]. However, based on the present results, we propose that this relationship may be not as simple as previously expected, and that memantine may actually protect against the cognitive impairments that accompany the onset of VDD, possibly by regulating the intra-neuronal calcium homeostasis which is affected during VDD. In all cases, these findings strengthen the need to prevent VDD, and

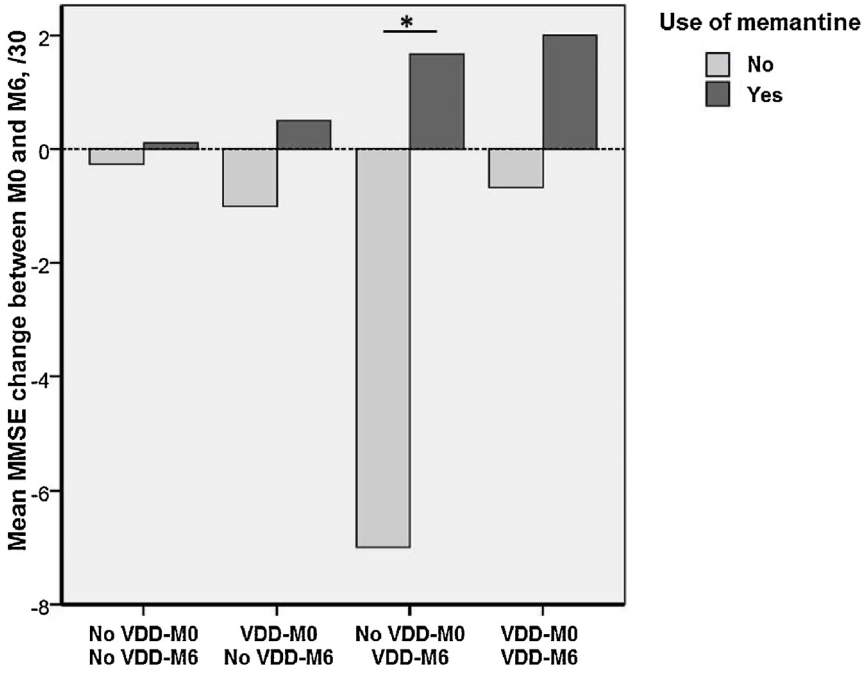

Fig. 2. Mean change in MMSE score between M0 and M6 according to the use of memantine and the presence of vitamin D deficiency (VDD) at M0 and M6 (n = 58). M0: month 0; M6: month 6; MMSE: Mini-Mental State Examination; *: P = 0.039

Table 3
Age-adjusted linear regression models showing the associations between the use of memantine (independent variable) and the change in MMSE score between M0 and M6 (dependent variable) according to vitamin D deficiency (VDD) at M0 and M6 (n = 58).

Use of memantine	Change in MMSE score between M0 and M6		
	β	[95%CI]	P-value
in Group 1 (No VDD-M0; No VDD-M6)	0.43	[−2.25; 3.10]	0.747
in Group 2 (VDD-M0; No VDD-M6)	1.41	[−3.26; 6.07]	0.499
in Group 3 (No VDD-M0; VDD-M6)	8.79	[1.06; 16.52]	**0.044**
in Group 4 (VDD-M0; VDD-M6)	2.56	[−2.41; 7.53]	0.157

β: coefficient of regression corresponding to a MMSE score between M0 and M6; CI: confidence interval; M0: month 0; M6: month 6; MMSE: Mini-Mental State Examination; VDD: vitamin D deficiency; coefficient of regression beta significant (i.e., $P < 0.05$) indicated in bold.

prompt to give memantine together with vitamin D supplement to AD patients.

Previous preclinical literature underlines the complementary and possibly synergistic effects of memantine and vitamin D in AD. Learning and memory difficulties in AD are partially explained by the glutamatergic excitotoxicity resulting in increased excitation of extrasynaptic NMDA receptors, excessive entry of calcium into the postsynaptic neuron, and ultimately glutamatergic neuronal death [5]. In patients treated with memantine, the binding of memantine on NMDA receptors with low affinity and rapid withdrawal kinetics reduces the excessive entry of calcium into the neuron and partially prevents neuronal death [3,10]. However, the constrained but persistent calcium entry ultimately causes oxidative stress and neuronal apoptosis, which justifies seeking to prevent initiation of the apoptotic cascade. Growing evidence precisely suggests that vitamin D has antioxidant effects by controlling intracellular free radicals generated by the reactive species of oxygen [9] and nitric oxide [23], and by inhibiting the synthesis of inducible nitric oxide synthase [24] and regulating the activity of the γ-glutamyl transpeptidase [25], a key enzyme of the antioxidant metabolism of glutathione. In addition, vitamin D also regulates the intra-neuronal calcium homeostasis [10], the inflammatory changes in the hippocampus [8], and the genetic expression of neurotrophic agents [26], i.e. defense mechanisms complementary to the action of memantine to increase neuroprotection in AD.

Some limitations of this study need to be considered. Firstly, the limited number of participants may be unrepresentative of the general population of AD patients. The study took place in one single memory clinic, and its retrospective design might have limited the number of patients includable. As this analysis was not initially planned, no concerted efforts were made at the time of the consultations to systematically give patients memantine, and to measure serum 25OHD status. The lack of power may explain the nonsignificant effects of memantine in Group 4 (patient with VDD at M0 and M6) and Group 2 (VDD at M0 and no VDD at M6). Secondly, although we were able to control for the age, other characteristics likely to modify the association between the use of memantine and the change of the MMSE score might still be present. Thirdly, an additional limitation lies in the failure to consider other dementias including vascular dementias.

5. Conclusions

We found that the use of memantine was associated with improved cognitive performance after 6 months of treatment only in the event of vitamin D deficiency at M6. This pilot study raises the hypothesis that memantine might prevent the cognitive decline that accompanies the onset of vitamin D deficiency. This result should be considered with caution due to the small sample size of the studied sample and the intrinsic biases of exposed/unexposed studies. A double-blind randomized placebo-controlled parallel group intent-to-treat superiority clinical trial, such as the AD-IDEA trial (Alzheimer's Disease-Input of Vitamin D with mEmantine Assay) [27], will help to determine whether the combination of memantine plus vitamin D prevents cognitive decline better than memantine alone in AD patients.

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