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Original Article

Clinical effects and mechanisms of risperidone and olanzapine in Alzheimer's disease

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Abstract: Objective: The aim of this study was to compare the clinical effects of risperidone and olanzapine in Alzheimer's disease (AD), exploring the possible mechanisms. Methods: A total of 172 AD patients, admitted from June 2016 to January 2018, were recruited for this prospective analysis. According to the use of drugs at admission, patients were assigned into the olanzapine group (n = 89) and risperidone group (n = 83). Patients were assessed, at study baseline (T0) and after 2 weeks (T1), 4 weeks (T2), and 8 weeks (T3), using the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), Positive and Negative Syndrome Scale (PANSS), total effective rates of treatment, and incidence of adverse reactions. Venous blood was drawn from the patients to determine expression levels of superoxide dismutase (SOD) and malondialdehyde (MDA) in serum using enzyme-linked immunosorbent assay. Results: BEHAVE-AD and PANSS scores at T1, T2, and T3, in both groups, were lower than those at T0, with scores at T3 the lowest. This was followed by scores at T2 (all $P < 0.001$). There were no significant differences between the two groups in total effective rates of treatment and incidence of adverse reactions (both $P > 0.050$). At T0 and T3, there were no significant differences between the two groups in expression levels of SOD and MDA (both $P > 0.050$). At T1 and T2, the olanzapine group was significantly higher than the risperidone group in SOD levels (both $P < 0.001$) and significantly lower than the risperidone group in MDA levels (both $P < 0.001$). SOD levels were significantly higher at T1, T2, and T3 than that at T0, in both groups (all $P < 0.001$), with the highest at T3. This was followed by SOD levels at T2 ($P < 0.001$). MDA levels were significantly lower at T1, T2, and T3 than that at T0, in both groups (all $P < 0.001$), with the lowest at T3. This was followed by MDA levels at T2 ($P < 0.001$). Regarding BEHAVE-AD and PANSS scores and SOD and MDA levels, the two groups were significantly different between T0 and T1 and between T2 and T3 (all $P < 0.001$). Levels were not significantly different between T1 and T2 (all $P > 0.050$). Conclusion: The use of olanzapine or risperidone for treatment of AD patients is clinically valuable. Both drugs can significantly improve psychiatric and behavioral symptoms and behavioral issues. However, olanzapine is better than risperidone, requiring less time to take effect.

Keywords: Olanzapine, risperidone, Alzheimer's disease, superoxide dismutase, malondialdehyde

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease [1]. AD patients mainly present with symptoms including agnosia, continuous decline in memory, aphasia, and behavioral issues [2]. The number of AD patients has increased along with the aging population in modern society [3]. AD can be classified into three stages, mild, moderate, and severe, according to patient mental states and conditions [4]. Statistics have shown there is at least one patient with mild AD in every 10 people aged over 60 years [5].

At present, the major therapy for AD aims at controlling psychiatric symptoms and improving their cognitive function, with typical medications including antipsychotics, cerebral metabolic enhancers, and neurotransmitter drugs [6-8]. With the increasing use of these therapeutic drugs, a growing number of studies in China or other countries have pointed out that conventional drugs may cause secondary damage to cognitive function during treatment of AD, resulting in occurrence of extrapyramidal symptoms [9-11]. Therefore, researchers have been committed to developing new methods of treatment of AD. It has been proven that atypical antipsychotics are safer than other drugs, with the same effects of controlling mental conditions [12]. Olanzapine and risperidone are the two representatives of atypical antipsychotics that have been widely used in treatment of AD.

However, there have been few studies focused on comparing the clinical efficacy between olanzapine and risperidone in AD. Even fewer studies have focused on the mechanisms of olanzapine and risperidone in AD.

Levels of superoxide dismutase (SOD) and malondialdehyde (MDA) will significantly change in oxidative stress. Therefore, they are important markers for oxidative stress and fundamental to human health. Moreover, they can be used as effective indicators for monitoring the severity of AD [13]. To understand the efficacy of olanzapine and risperidone in the treatment of AD, this study recruited patients to compare differences in behavioral issues and clinical efficacy. In addition, this study examined the mechanisms of the two drugs, aiming to provide guidance for clinical treatment.

Materials and methods

General information

A total of 172 AD patients, admitted to The Second Xiangya Hospital of Central South University, from June 2016 to January 2018, were recruited for prospective analysis.

Inclusion criteria: Patients meeting diagnostic criteria according to guidelines for Alzheimer's disease in 2015 [14]; Patients with mental disorders of different stages; Patients that received subsequent therapy of olanzapine or risperidone in the Second Xiangya Hospital of Central South University after diagnosis; Patients aged 30-90 years; Patients with a complete case history. A total of 329 patients were initially enrolled in this study, in accordance with inclusion criteria.

Exclusion criteria: Patients with tumors; Patients with organ failure; Patients with other hematologic diseases; Patients with other immunological disorders; Patients that were physically disabled; Patients that were bedridden; Patients that were pregnant; Patients that received other antipsychotics before the study; Patients with drug allergies; Patients complicated with several mental disorders; Patients transferred from other hospitals. A total of 172 patients were finally recruited into this study, according to inclusion and exclusion criteria. Of these, 94 were male and 78 were female. Ages ranged from 59 to 82 years, with a mean age of 71.7 years (sd = 6.8).

Methods

According to the use of drugs at admission, patients were assigned into the olanzapine group (n = 89) and risperidone group (n = 83). Olanzapine (5 mg per tablet, lot: H20160497) was purchased from Lilly del Caribe Inc. (Indianapolis, USA). The dose of 10 mg once a day was recommended, initially, then was adjusted according to clinical response to 5-20 mg once a day. The usual dose was 10 mg daily. Doses greater than 10 mg once a day were only available after clinical assessment. Risperidone (2 mg per tablet, lot: H20010310) was purchased from Xi'an-Janssen Pharmaceutical Ltd. (China). The initial dose was 2 mg once a day. The dose was gradually increased to 4 mg once a day after one week. The dose could be gradually increased to 6 mg daily in the second week and was maintained in the following weeks or adjusted according to individual response. A dose of 6 mg daily was recommended. The maximum dose should be no more than 10 mg daily. The duration of treatment for the two groups was 8 weeks. Measurements were carried out at study baseline (T0) and after 2 weeks (T1), 4 weeks (T2), and 8 weeks (T3) of treatment. A total of 4 mL of morning fasting venous blood was used to determine expression levels of SOD and MDA.

Enzyme-linked immunosorbent assay (ELISA)

Venous blood was kept at room temperature for 30 minutes and subsequently centrifuged for 10 minutes to obtain the serum. Expression levels of SOD and MDA were detected by ELISA using the serum. SOD ELISA kits (ZC-32619) were purchased from ZCi Bio (Shanghai, China). MDA ELISA kits (DL-MDA-Ge1) were purchased from Wuxi Donglin Sci & Tech Development Co., Ltd. (China). The ELISA analyzer (HBS-1101) was purchased from Nanjing DeTie Experimental Equipment Co., Ltd. (China). The procedure strictly complied with manufacturer instructions. Standards were prepared and a standard curve was for every experiment. Wells for the subtraction of background absorbance, or blank wells, were recommended for every plate. Blank wells contained only TMB and stop solution. Differences in absorbance values of the duplicate wells were within 20%. The OD of the blank well was subtracted from the OD of each standard or sample (no subtraction was needed if no blank well was prepared). Results are

Table 1. Comparison of baseline characteristics between the two groups (n, %)

	The olanzapine group (n = 89)	The risperidone group (n = 83)	t/χ^2	P
Age (year)	72.4±6.9	71.9±7.1	0.468	0.640
Weight (kg)	67.24±11.24	68.37±12.57	0.622	0.535
Body mass index	19.81±5.24	18.73±5.68	1.297	0.196
Duration of disease (week)	5.26±2.86	5.64±2.98	0.853	0.395
Gender			0.174	0.677
Male	50 (56.18)	44 (53.01)		
Female	39 (43.82)	39 (46.99)		
Number of families			0.171	0.680
1-2	64 (71.91)	62 (74.70)		
> 2	25 (28.09)	21 (25.30)		
Places of living			0.212	0.645
Urban areas	75 (84.27)	72 (86.75)		
Rural areas	14 (15.73)	11 (13.25)		
Smoking			0.466	0.495
Yes	56 (62.92)	48 (57.83)		
No	33 (37.08)	35 (42.17)		
Alcohol use			0.166	0.684
Yes	51 (57.30)	45 (54.22)		
No	38 (42.70)	38 (45.78)		
Exercise habit			0.474	0.491
Yes	21 (23.60)	16 (19.28)		
No	68 (76.40)	67 (80.72)		
Pre-treatment BEHAVE-AD	28.69±5.48	28.54±5.77	0.175	0.861
Pre-treatment PANSS	89.62±8.49	90.24±8.67	0.474	0.636

Note: BEHAVE-AD: Behavioral Pathology in Alzheimer's Disease Rating Scale; PANSS: Positive and Negative Syndrome Scale.

expressed by the mean optical density (OD) of duplicate wells. The standard curve was ploted. The corresponding concentration of a sample was calculated using its OD and the standard curve. If the OD of a sample exceeded the upper limit of the standard curve, it was remeasured after proper dilution. Calculation of concentrations was then completed after multi pling the dilution factor of that sample.

Measurements

Baseline characteristics were recorded and compared between the two groups, including age, gender, weight, and family environment.

Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD): This is a 25-item scale developed by Reisberg et al., designed to assess non-cognitive behavioral disorders in AD patients [15]. It consists of 7 subscales, with symptoms rated on a 4-point severity scale, ranging from 0 to 3.

Positive and Negative Syndrome Scale (PANSS): According to Schmidt et al., patient post-treatment PANSS scores are defined as follows: higher than 75% excellent; from 50%-75%, effective; from 25%-50%, common; lower than 25%, ineffective [16]. Total effective rate = (cases of excellent + cases of effective + cases of common)/total cases * 100%.

Incidence of adverse reactions: Adverse drug reactions, during treatment, were recorded. Incidence of adverse reactions = cases of adverse reactions/total cases * 100%. All results were rounded to the second decimal place.

Statistical analysis

Data were statistically processed using SPSS 24.0 software package (Shanghai Yuchuang Network Technology Co; Ltd). Measurement data are expressed as mean ± standard deviation ($\bar{x}$ ± sd). Comparisons within the group, before and after treatment, were based on paired t-tests. Comparisons between the two groups were conducted using independent-sample t-tests. Enumeration data are expressed as cases/percentage (n/%). Incidence of adverse reactions was compared with Fisher's exact test and total effective rates of treatment were compared using nonparametric test. $P < 0.05$ indicates statistical significance.

Results

Baseline characteristics

The two groups were compared regarding baseline characteristics, including age, weight, body mass index, duration of disease, gender, family information, place of living, smoking, alcohol

Table 2. Comparison of BEHAVE-AD scores between the two groups

	The olanzapine group (n = 89)	The risperidone group (n = 83)	t	P
Score				
T0	28.69±5.48	28.54±5.77	0.175	0.861
T1	19.83±4.25	25.63±4.51	8.683	< 0.001
T2	13.28±3.59	18.77±4.05	9.421	< 0.001
T3	7.16±2.08	7.25±2.12	0.779	0.281
Difference				
T1-T0	-8.86±4.14	-2.91±3.94	9.640	< 0.001
T2-T1	-6.55±4.57	-6.86±3.15	0.514	0.608
T3-T2	-6.12±2.17	-11.52±2.98	13.65	< 0.001

Note: BEHAVE-AD: Behavioral Pathology in Alzheimer's Disease Rating Scale. T0: at study baseline; T1: after 2 weeks; T2: 4 weeks; T3: 8 weeks.

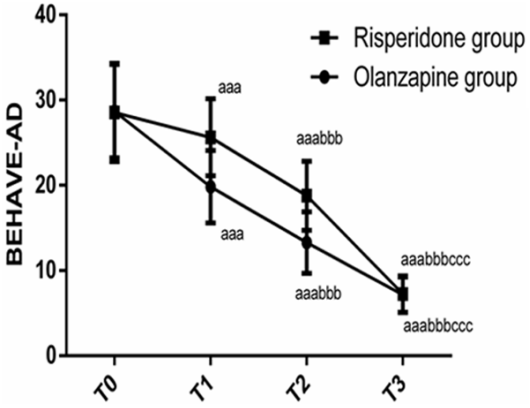

Figure 1. Comparison of BEHAVE-AD scores between the two groupsCompared with the BEHAVE-AD score at T0 within the group, $^{aaa}P < 0.001$; Compared with the BEHAVE-AD score at T1 within the group, $^{bbb}P < 0.001$; Compared with the BEHAVE-AD score at T2 within the group, $^{ccc}P < 0.001$. BEHAVE-AD: Behavioral Pathology in Alzheimer's Disease Rating Scale. T0: at study baseline; T1: after 2 weeks; T2: 4 weeks; T3: 8 weeks.

use, exercise habits, pre-treatment BEHAVE-AD, and PANSS scores. No significant differences were found in baseline characteristics between the two groups (all P > 0.050), indicating that the two groups were comparable. See **Table 1**.

Comparison of BEHAVE-AD scores

There were no significant differences in BEHAVE-AD scores between the two groups at T0 (P > 0.050). At T1, the BEHAVE-AD score in the olanzapine group was 19.83±4.25, significantly lower than the 25.63±4.51 in the risperidone group (P < 0.050). At T2, the BEHAVE-AD score in the olanzapine group was 13.28±3.59, significantly lower than the 18.77±4.05 in the risperidone group (P < 0.050). At T3, BEHAVE-AD scores were not significantly different between the two groups (P > 0.050). BEHAVE-AD scores at T1, T2, and T3, in both groups, were lower than that at T0, with scores at T3 the lowest. This was followed by scores at T2 (P < 0.001). Regarding BEHAVE-AD scores, the two groups were significantly different between T0 and T1 and between T2 and T3 (both P < 0.001), but were not significantly different between T1 and T2 (P > 0.050). See **Table 2** and **Figure 1**.

Comparison of PANSS scores

There were no significant differences in PANSS scores between the two groups at T0 (P > 0.050). At T1, the PANSS score in the olanzapine group was 62.33±7.86, significantly lower than the 76.16±8.04 in the risperidone group (P < 0.050). At T2, the PANSS score in the olanzapine group was 44.27±6.24, significantly lower than the 59.14±5.86 in the risperidone group (P < 0.050). At T3, PANSS scores were not significantly different between the two groups (P > 0.050). PANSS scores at T1, T2, and T3, in both groups, were lower than that at T0, with scores at T3 the lowest. This was followed by scores at T2 (P < 0.001). Concerning PANSS scores, the two groups were significantly different between T0 and T1 and between T2 and T3 (both P < 0.001), but were not significantly different between T1 and T2 (P > 0.050). See **Table 3** and **Figure 2**.

Comparison of incidence of adverse reactions

In the olanzapine group, the total incidence of adverse reactions was 7.86%. Fatigue accounted for 1.12% (1 case), lethargy for 1.12% (1 case), visual impairment for 2.25% (2 cases), headache for 1.12% (1 case), and abnormal liver function for 2.25% (2 cases). In the risperidone group, the total incidence of adverse reactions was 7.23%. Lethargy accounted for 1.20% (1 case), insomnia for 1.20% (1 case), visual impairment for 1.20% (2 cases), and extrapyramidal symptoms for 2.41% (2 cases). No significant differences were found in incidence of adverse reactions between the two groups (P > 0.050). See **Table 4**.

Table 3. Comparison of PANSS scores between the two groups

	The olanzapine group (n = 89)	The risperidone group (n = 83)	t	P
Score				
T0	89.62±8.49	90.24±8.67	0.474	0.636
T1	62.33±7.86	76.16±8.04	11.402	< 0.001
T2	44.27±6.24	59.14±5.86	16.081	< 0.001
T3	38.71±5.06	39.16±5.14	0.578	0.564
Difference				
T1-T0	-27.29±6.89	-14.08±8.12	11.532	< 0.001
T2-T1	-18.06±5.18	-17.02±6.54	1.160	0.248
T3-T2	-5.56±5.04	-19.98±5.98	17.143	< 0.001

Note: PANSS: Positive and Negative Syndrome Scale. T0: at study baseline; T1: after 2 weeks; T2: 4 weeks; T3: 8 weeks.

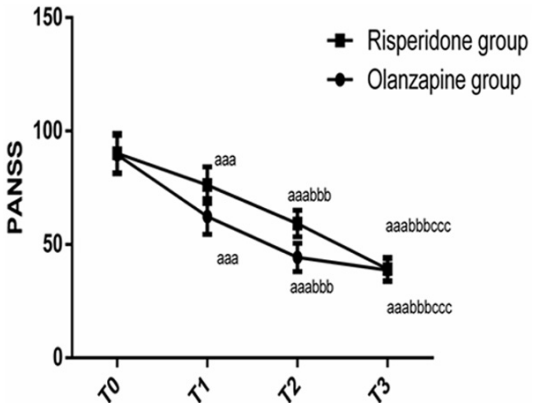

Figure 2. Comparison of PANSS scores between the two groups Compared with the PANSS score at T0 within the group, $^{aaa}P < 0.001$; Compared with the PANSS score at T1 within the group, $^{bbb}P < 0.001$; Compared with the PANSS score at T2 within the group, $^{ccc}P < 0.001$. PANSS: Positive and Negative Syndrome Scale. T0: at study baseline; T1: after 2 weeks; T2: 4 weeks; T3: 8 weeks.

Comparison of effective rates of treament

Effective rates of treatment were 85.39% in the olanzapine group and 87.95% in the risperidone group. There were no significant differences between the two groups in effective rates of treatment (P > 0.050). See **Table 5**.

Comparison of SOD and MDA levels

There were no significant differences in SOD and MDA levels between the two groups at T0 (P > 0.050). At T1, the olanzapine group had a significantly higher SOD level and a significantly lower MDA level than the risperidone group (both P < 0.001). At T2, the olanzapine group was significantly higher in SOD levels and lower in MDA levels than the risperidone group (both P < 0.001). At T3, the groups were not significantly different in SOD and MDA levels (P > 0.050). SOD levels were significantly higher at T1, T2, and T3 than that at T0, in both groups (all P < 0.001), with the highest at T3. This was followed by SOD levels at T2 (P < 0.001). MDA levels were significantly lower at T1, T2, and T3 than that at T0, in both groups (all P < 0.001), with the lowest at T3. This was followed by MDA levels at T2 (P < 0.001). The two groups were significantly different in SOD levels between T0 and T1 and between T2 and T3 (both P < 0.001), but were not significantly different between T1 and T2 (P > 0.050). The two groups were significantly different in MDA levels between T0 and T1, between T1 and T2, and between T2 and T3 (both P < 0.001). See **Tables 6**-**9**, **Figures 3** and **4**.

Discussion

The pathogenesis of AD remains unclear at present. Many studies in China and other countries have stated that occurrence of AD is closely associated with neurotransmitter imbalances, inflammation, and free radical damage [17-19]. The rising prevalence of AD has called for more clinical effort in this field. Over 80% of AD patients have presented with psychiatric and behavioral symptoms. In the current treatment of AD, rehabilitation of psychiatric and behavioral symptoms is as crucial as improvements in cognitive function [20]. Studies have shown that β-amyloid deposition and neurofibrillary tangles can result in a considerable decrease in the number of neurons in patients with development of AD. Moreover, it can reduce levels of acetylcholine, a neurotransmitter that has an important bearing on memory and learning ability [21, 22]. Given the above problems, atypical antipsychotics, including olanzapine and risperidone, have been developed for treatment of AD. Their therapeutic effects have been confirmed. Olanzapine, a thienobenzodiazepine derivative, is a novel antipsychotic agent that reduces dopamine secretion by blocking dopamine D2 and serotonin 5-HT_{2A} receptors. It also has a high affinity with histamine and dopamine D receptors and is less likely to induce side effects [23]. Risperidone, a benzoxazole derivative, is a selective

Table 4. Comparison of incidence of adverse reactions between the two groups (n, %)

	The olanzapine group (n = 89)	The risperidone group (n = 83)	χ^2	P
Fatigue	1 (1.12)	0 (0.00)	0.938	0.333
Lethargy	1 (1.12)	1 (1.20)	0.002	0.960
Insomnia	0 (0.00)	1 (1.20)	1.079	0.299
Visual impairment	2 (2.25)	1 (1.20)	0.272	0.602
Headache	1 (1.12)	0 (0.00)	0.938	0.333
Extrapyramidal symptoms	0 (0.00)	2 (2.41)	2.170	0.141
Abnormal liver function	2 (2.25)	0 (0.00)	1.887	0.170
Incidence of adverse reactions (%)	7 (7.87)	5 (6.02)	0.224	0.636

Table 5. Comparison of effective rates of treatment between the two groups

	The olanzapine group (n = 89)	The risperidone group (n = 83)	Z	P
Excellent	35 (39.33)	32 (38.55)		
Effective	25 (28.09)	27 (32.53)		
Common	16 (17.98)	14 (16.87)		
neffective	13 (14.61)	10 (12.05)		
Effective rate of treatment (%)	85.39	87.95	-0.368	0.713

Table 6. Comparison of SOD levels between the two groups (U/mL)

	The olanzapine group (n = 89)	The risperidone group (n = 83)	t	P
T0	86.73±12.87	87.54±11.97	0.427	0.670
T1	124.63±15.24	107.69±13.43	7.712	< 0.001
T2	153.81±11.69	134.20±12.08	10.823	< 0.001
T3	168.74±8.69	166.98±9.27	1.285	0.201

Note: SOD: superoxide dismutase. T0: at study baseline; T1: after 2 weeks; T2: 4 weeks; T3: 8 weeks.

Table 7. Comparison of differences of SOD levels between the two groups (U/mL)

	The olanzapine group (n = 89)	The risperidone group (n = 83)	t	P
T1-T0	37.90±13.84	20.15±11.86	9.000	< 0.001
T2-T1	29.18±12.63	26.51±12.14	1.412	0.160
T3-T2	14.93±9.16	32.78±10.16	12.123	< 0.001

Note: SOD: superoxide dismutase. T0: at study baseline; T1: after 2 weeks; T2: 4 weeks; T3: 8 weeks.

monoaminergic antagonist with a high affinity for serotonin 5-HT and dopmine D receptors [24]. Presently, olanzapine and risperidone are widely used in the treatment of AD. The purpose of this study was to compare the efficacy between olanzapine and risperidone, exploring the benefits and harms of their use in the treatment of AD patients. This study aimed to provide more accurate reference for clinical selection of therapeutic drugs in the future.

Results of this study showed that BEHAVE-AD and PANSS scores in the olanzapine group were significantly lower than those in the risperidone group at T1 and T2. This indicates that olanzapine requires less time to take effect, compared with risperidone. The possible reason for this is that olanzapine acts as antagonist to dopamine D_2 and D_3, and serotonin 5-HT_2 receptors, which can selectively increase concentrations of acetylcholine in brain tissues of patients [25]. However, risperidone has a relatively low affinity for histmine H_1 and α_2-adrenergic receptors and no affinity for acetycholine receptors [26]. Therefore, risperidone cannot fully play its role as an antagonist in AD patients, leading to slow rehabilitation. For BEHAVE-AD and PANSS scores, the two groups were significantly different in the two scores between T0 and T1 and between T2 and T3, but were not significantly different between T1 and T2. This may be attributable to

Table 8. Comparison of MDA levels between the two groups (mmol/mL)

	The olanzapine group (n = 89)	The risperidone group (n = 83)	t	P
T0	28.74±3.65	28.64±3.72	0.178	0.859
T1	17.92±2.15	21.69±2.27	11.192	< 0.001
T2	12.68±2.28	15.84±2.04	9.554	< 0.001
T3	6.53±1.16	6.62±1.20	0.500	0.618

Note: MDA, malondialdehyde. T0: at study baseline; T1: after 2 weeks; T2: 4 weeks; T3: 8 weeks.

Table 9. Comparison of differences of MDA levels between the two groups (mmol/mL)

	The olanzapine group (n = 89)	The risperidone group (n = 83)	t	P
T1-T0	-10.82±2.86	-6.95±2.52	9.404	< 0.001
T2-T1	-5.24±1.86	-5.85±1.96	2.094	0.038
T3-T2	-6.15±1.54	-9.22±1.04	15.213	< 0.001

Note: MDA, malondialdehyde. T0: at study baseline; T1: after 2 weeks; T2: 4 weeks; T3: 8 weeks.

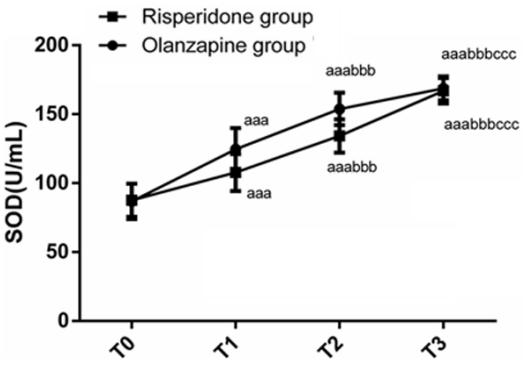

Figure 3. Comparison of SOD levels between the two groups,Compared with the SOD level at T0 within the group, $^{aaa}P < 0.001$; Compared with the SOD level at T1 within the group, $^{bbb}P < 0.001$; Compared with the SOD level at T2 within the group, $^{ccc}P < 0.001$. SOD, superoxide dismutase. T0: at study baseline; T1: after 2 weeks; T2: 4 weeks; T3: 8 weeks.

the rapid therapeutic effects of olanzapine for AD, which produce visible results at T1. The downward trend of its therapeutic effects at T2 and T3 may be the result of the relatively short half-life of olanzapine. However, the treatment effects were lower in the risperidone group than in the olanzapine group at T1. Effects in the risperidone group increased at T2 and T3. Comparing the differences in BEHAVE-AD and PANSS scores between the two groups, it was found that olanzapine achieved visible effects after 2 weeks of treatment, while risperidone required 4 weeks of treatment to show significant effects. Comparison of effective rates between the two groups revealed no significant differences. This suggests that the two drugs are both valuable for treatment of AD, consistent with the findings of Cummings et al. [27]. Comparing incidence of adverse reactions between the two groups showed no significant differences. However, there were 2 cases of extrapyramidal symptoms in the risperidone group and none in the olanzapine group. The reason is that olanzapine mainly acts on the midbrain limbic area and midbrain cortical areas. It has minimal impact on the nigrostriatal pathway, thereby maximally reducing the possibility of extrapyramidal symptoms [28]. The extensive hepatic metabolisms of olanzapine may be the cause of increased rates of abnormal liver function in the olanzapine group [29]. Risperidone has a relatively long half-life after oral administration [30]. Increased dosage may cause the rise of drug plasma concentrations due to the plasma protein binding of risperidone. Given the low clearance rate in patients, a series of adverse reactions may occur. The lack of statistically significant differences in incidence of adverse reactions between the two groups may be due to the small population of study subjects.Infuturestudies,samplesizesshouldbeincreased to obtain more accurate data.

To explore the therapeutic mechanisms of olanzapine and risperidone in AD, this study further analyzed changes in SOD and MDA levels in AD patients treated with olanzapine and risperidone. The olanzapine group was significantly higher in SOD levels and significantly lower in MDA levels than the risperidone group at T1 and T2. MDA, an indicator of oxidative stress, is generally highly expressed upon occurrence of AD [31]. Many free radicals in the brain tissue cause a considerable increase of lipid peroxidation, thereby reducing synthesis in cells, as well as weakening the activity of SOD. SOD is an antioxidant enzyme that catalyzes the dismutation of superoxide anion radicals. It acts as an effective protector for the normal function of cells and tissues [32]. This suggests that olanzapine may treat AD by interacting with SOD and MDA in patients. The precise mechanisms of olanzapine require further experimentation.

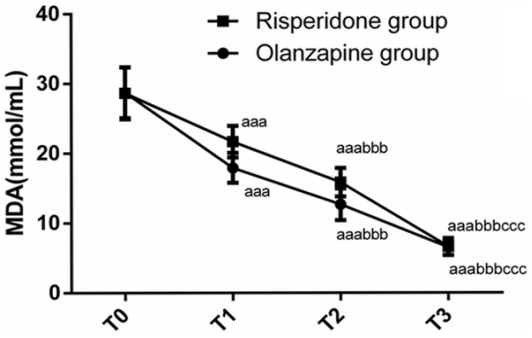

Figure 4. Comparison of MDA levels between the two groups Compared with the MDA level at T0 within the group, $^{aaa}P < 0.001$; Compared with the MDA level at T1 within the group, $^{bbb}P < 0.001$; Compared with the MDA level at T2 within the group, $^{ccc}P < 0.001$. MDA: malondialdehyde. T0: at study baseline; T1: after 2 weeks; T2: 4 weeks; T3: 8 weeks.

This study was designed to compare differences in efficacy between olanzapine and risperidone in the treatment of AD. However, there were a few limitations due to insufficient experimental conditions. First, the study population was small. Therefore, statistical analysis based on big data could not be performed. Second, the composition of the study population was relatively simple in ethnicity, without considering possible differences in other populations. Third, the drugs used in this study may have differences with other drugs of this kind produced by other pharmaceutical companies (such as risperidone, available in both tablets and oral solution). Longer-term follow-ups should be conducted to obtain the best experimental results.

In conclusion, the use of olanzapine or risperidone for treatment of AD is clinically valuable, as both drugs can both significantly improve psychiatric and behavioral symptoms and behavioral issues. However, olanzapine is better than risperidone, requiring less time to take effect.

Disclosure of conflict of interest

None.

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References

[1] Van Cauwenberghe C, Van Broeckhoven C and Sleegers K. The genetic landscape of Alzheimer disease: clinical implications and perspectives. Genet Med 2016; 18: 421-430.

[2] Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Feldman HH, Frisoni GB, Hampel H, Jagust WJ, Johnson KA, Knopman DS, Petersen RC, Scheltens P, Sperling RA, Dubois B. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology 2016; 87: 539-547.

[3] van de Haar HJ, Burgmans S, Jansen JF, van Osch MJ, van Buchem MA, Muller M, Hofman PA, Verhey FR, Backes WH. Blood-brain barrier leakage in patients with early Alzheimer disease. Radiology 2017; 282: 615.

[4] Roberts RO, Christianson TJ, Kremers WK, Mielke MM, Machulda MM, Vassilaki M, Alhurani RE, Geda YE, Knopman DS, Petersen RC. Association between olfactory dysfunction and amnestic mild cognitive impairment and Alzheimer disease dementia. JAMA Neurol 2016; 73: 93-101.

[5] Wang L, Benzinger TL, Su Y, Christensen J, Friedrichsen K, Aldea P, McConathy J, Cairns NJ, Fagan AM, Morris JC, Ances BM. Evaluation of tau imaging in staging Alzheimer disease and revealing interactions between β-amyloid and Tauopathy. JAMA Neurol 2016; 73: 1070-1077.

[6] Folch J, Petrov D, Ettcheto M, Abad S, Sánchez-López E, García ML, Olloquequi J, Beas-Zarate C, Auladell C, Camins A. Current research therapeutic strategies for Alzheimer's disease treatment. Neural Plast 2016; 2016: 8501693.

[7] Loureiro JA, Gomes B, Fricker G, Coelho MAN, Rocha S, Pereira MC. Cellular uptake of plga-nanoparticles targeted with anti amyloid and anti transferrin receptor antibodies for Alzheimer's disease treatment. Colloids Surf B Biointerfaces 2016; 145: 8-13.

[8] Reiman EM, Langbaum JB, Tariot PN, Lopera F, Bateman RJ, Morris JC, Sperling RA, Aisen PS, Roses AD, Welsh-Bohmer KA, Carrillo MC, Weninger S. CAP--advancing the evaluation of preclinical Alzheimer disease treatments. Nat Rev Neurol 2016; 12: 56-61.

[9] Gejl M, Gjedde A, Egefjord L, Møller A, Hansen SB, Vang K, Rodell A, Brændgaard H, Gottrup H, Schacht A, Møller N, Brock B, Rungby J. In Alzheimer's disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: randomized, placebo-controlled, double-blind clinical trial. Front Aging Neurosci 2016; 8: 108.

[10] Siemers ER, Sundell KL, Carlson C, Case M, Sethuraman G, Liu-Seifert H, Dowsett SA, Pon-

tecorvo MJ, Dean RA, Demattos R. Phase 3 solanezumab trials: secondary outcomes in mild Alzheimer's disease patients. Alzheimers Dement 2016; 12: 110-120.

[11] O'Bryant SE, Mielke MM, Rissman RA, Lista S, Vanderstichele H, Zetterberg H, Lewczuk P, Posner H, Hall J, Johnson L, Fong YL, Luthman J, Jeromin A, Batrla-Utermann R, Villarreal A, Britton G, Snyder PJ, Henriksen K, Grammas P, Gupta V, Martins R, Hampel H; Biofluid Based Biomarker Professional Interest Area. Blood-based biomarkers in Alzheimer disease: current state of the science and a novel collaborative paradigm for advancing from discovery to clinic. Alzheimers Dement 2017; 13: 45-58.

[12] Nørgaard A, Jensen-Dahm C, Gasse C, Hansen HV, Waldemar G. Time trends in antipsychotic drug use in patients with dementia: a nationwide study. J Alzheimers Dis 2016; 49: 211-220.

[13] Farlow MR, Shamliyan TA. Benefits and harms of atypical antipsychotics for agitation in adults with dementia. Eur Neuropsychopharmacol 2017; 27: 217-231.

[14] Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, Bakardjian H, Benali H, Bertram L, Blennow K, Broich K, Cavedo E, Crutch S, Dartigues JF, Duyckaerts C, Epelbaum S, Frisoni GB, Gauthier S, Genthon R, Gouw AA, Habert MO, Holtzman DM, Kivipelto M, Lista S, Molinuevo JL, O'Bryant SE, Rabinovici GD, Rowe C, Salloway S, Schneider LS, Sperling R, Teichmann M, Carrillo MC, Cummings J, Jack CR Jr; Proceedings of the Meeting of the International Working Group (IWG) and the American Alzheimer's Association on "The Preclinical State of AD"; July 23, 2015; Washington DC, USA. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. Alzheimers Dement 2016; 12: 292-323.

[15] Reisberg B, Auer SR and Monteiro IM. Behavioral pathology in Alzheimer's disease (BEHAVE-AD) rating scale. Int Psychogeriatr 1996; 8 Suppl 3: 301-8; discussion 351-4.

[16] Schmidt E, Areberg J. Methods of treating alzheimer's disease and pharmaceutical compositions thereof: U.S. Patent 9,375,418. 2016-6-28.

[17] Marsh SE, Abud EM, Lakatos A, Karimzadeh A, Yeung ST, Davtyan H, Fote GM, Lau L, Weinger JG, Lane TE, Inlay MA, Poon WW and Blurton-Jones M. The adaptive immune system restrains Alzheimer's disease pathogenesis by modulating microglial function. Proc Natl Acad Sci USA 2016; 113: E1316-1325.

[18] Atwood CS, Huang X, Moir RD, Tanzi RE and Bush AI. Role of free radicals and metal ions in the pathogenesis of Alzheime's disease. Met Ions Biol Syst 1999; 36: 309-364.

[19] Tramutola A, Lanzillotta C, Perluigi M and Butterfield DA. Oxidative stress, protein modification and Alzheimer disease. Brain Res Bull 2017; 133: 88-96.

[20] Kamat PK, Kalani A, Rai S, Swarnkar S, Tota S, Nath C and Tyagi N. Mechanism of oxidative stress and synapse dysfunction in the pathogenesis of Alzheimer's disease: understanding the therapeutics strategies. Mol Neurobiol 2016; 53: 648-661.

[21] Gordon BA, Blazey T, Su Y, Fagan AM, Holtzman DM, Morris JC, Benzinger TL. Longitudinal β-amyloid deposition and hippocampal volume in preclinical Alzheimer disease and suspected Non-Alzheimer disease pathophysiology. JAMA Neurol 2016; 73: 1192-1200.

[22] Deutsch SI, Burket JA, Benson AD and Urbano MR. The 15q13.3 deletion syndrome: deficient α7-containing nicotinic acetylcholine receptor mediated neurotransmission in the pathogesis of neurodevelopmental disorders. Prog Neuropsychopharmacol Biol Psychiatry 2016; 64: 109-117.

[23] Di Domenico F, Tramutola A, Butterfield DA. Role of 4-hydroxy-2-nonenal (HNE) in the pathogenesis of alzheimer disease and other selected age-related neurodegenerative disorders. Free Radic Biol Med 2017; 111: 253-261.

[24] Dadey E, Li Q and Lindemann C. Sustained delivery formulations of risperidone compounds: U.S. Patent Application 10/010,612. 2018-7-3.

[25] Yatham LN, Beaulieu S, Schaffer A, Kauer-Sant'Anna M, Kapczinski F, Lafer B, Sharma V, Parikh SV, Daigneault A and Qian H. Optimal duration of risperidone or olanzapine adjunctive therapy to mood stabilizer following remission of a manic episode: a CANMAT randomized double-blind trial. Mol Psychiatry 2016; 21: 1050-1056.

[26] Kraguljac NV, White DM, Hadley JA, Visscher K, Knight D, ver HL, Falola B and Lahti AC. Abnormalities in large scale functional networks in unmedicated patients with schizophrenia and effects of risperidone. Neuroimage Clin 2016; 10: 146-158.

[27] Cummings J, Lai TJ, Hemrungrojn S, Mohandas E, Yun KS, Nair G and Dash A. Role of donepezil in the management of neuropsychiatric symptoms in Alzheimer's disease and dementia with lewy bodies. CNS Neurosci Ther 2016; 22: 159-166.

[28] Larsen JR, Vedtofte L, MSL J, Jespersen HR, Jakobsen MI, Svensson CK, Koyuncu K, Schjerning O, Oturai PS, Kjaer A, Nielsen J, Holst JJ, Ekstrøm CT, Correll CU, Vilsbøll T and Fink-Jensen A. Effect of liraglutide treatment on prediabetes and overweight or obesity in

clozapine- or olanzapine-treated patients with schizophrenia spectrum disorder: a randomized clinical trial. JAMA Psychiatry 2017; 74: 719-728.

[29] Schoretsanitis G, Stegmann B, Hiemke C, Gründer G, Schruers KR, Walther S, Lammertz SE, Haen E and Paulzen M. Pharmacokinetic patterns of risperidone-associated adverse drug reactions. Eur J Clin Pharmacol 2016; 72: 1091-1098.

[30] Patel AN, Lee S, Andrews HF, Pelton GH, Schultz SK, Sultzer DL, Mintzer J, de la Pena D, Gupta S, Colon S, Schimming C, Levin B and Devanand DP. Prediction of relapse after discontinuation of antipsychotic treatment in Alzheimer's disease: the role of hallucinations. Am J Psychiatry 2017; 174: 362-369.

[31] Trist BG, Davies KM, Cottam V, Genoud S, Ortega R, Roudeau S, Carmona A, De Silva K, Wasinger V, SJG L, Sachdev P, Smith B, Troakes C, Vance C, Shaw C, Al-Sarraj S, Ball HJ, Halliday GM, Hare DJ and Double KL. Amyotrophic lateral sclerosis-like superoxide dismutase 1 proteinopathy is associated with neuronal loss in Parkinson's disease brain. Acta Neuropathol 2017; 134: 113-127.

[32] Dinh QN, Young MJ, Evans MA, Drummond GR, Sobey CG and Chrissobolis S. Aldosterone-induced oxidative stress and inflammation in the brain are mediated by the endothelial cell mineralocorticoid receptor. Brain Res 2016; 1637: 146-153.