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A comparative study of olanzapine, aripiprazole and risperidone in the treatment of psychiatric and behavioral symptoms of Alzheimer's disease

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Abstract: To investigate the efficacy and safety of olanzapine, aripiprazole, and risperidone in the treatment of mental and behavioral symptoms of Alzheimer's Disease. A retrospective analysis was performed on the clinical data of 126 patients with Alzheimer's Disease from February 2018 to February 2020. The patients were divided into group A (aripiprazole, n=44), group B (olanzapine, n=42) and group C (risperidone, n=40) based on the treatment method. Remarkably differences at different time points among the three groups were observed (P<0.05). Significant differences in the Positive and Negative Syndrome Scale scores of different time points and cross-group comparison among the three groups were detected (P<0.05). The time-point comparison of BEHAVE-AD scores among the three groups indicated a remarkable difference (P<0.05). After 4 weeks of treatment, the Positive and Negative Syndrome Scale and BEHAVE-AD scores of group A were lower than those of groups B and C (P<0.05). The total incidence of adverse reactions in group A was remarkably lower than in groups B and C (P<0.05). Olanzapine, aripiprazole and risperidone are effective in treating Alzheimer's disease and aripiprazole, with a better safety profile and fewer adverse reactions, is more suitable for elderly patients.

Keywords: Olanzapine, aripiprazole, risperidone, senile, dementia, psychiatric and behavioral disorders.

INTRODUCTION

Alzheimer's Disease (AD) is a disturbance of intelligence caused by brain dysfunction, featuring comprehensiveness and persistence (Keyong *et al*., 2017). Although the pathogenesis of AD has not been fully elucidated, it is considered to be related to neurotransmitter deficiency, inflammation, free radical injury, amyloid protein, hormone deficiency, and other related factors. Research (Han *et al*., 2018) pointed out that in addition to cognitive impairment, AD patients also experience severe mental and behavioral symptoms, such as depression, anxiety, hallucination and delusion, accompanied by aimless wandering, restlessness and aggression. Currently, olanzapine, aripiprazole and risperidone are the main drugs in clinical treatment. However, few clinical comparative studies have been conducted on the three drugs which have an elusive mechanism of action, to examine and compare their efficacy and safety. Therefore, this study identified the clinical data of 126 AD patients for retrospective analysis to explore the efficacy and safety of olanzapine, aripiprazole and risperidone in the treatment of psychiatric and behavioral symptoms of AD. It is reported as follows:

MATERIALS AND METHODS

Clinical data

The clinical data of 126 AD patients admitted to our hospital from February 2018 to February 2020 were retrospectively analyzed. Diagnostic criteria: in accordance with the diagnostic criteria for dementia in *2018* Chinese Guidelines for Diagnosis and Treatment of Dementia and Cognitive Impairment (2): Guidelines for Diagnosis and Treatment of AD (2018). Inclusion criteria: (1) Patients aged 60 and above; (2) Patients with no use of antipsychotic drugs before enrollment. (3) Patients with Behave-AD scores ≥8 points; (4) Patients with Positive and Negative Syndrome Scale (PANSS) scores ≥65 points. Exclusion criteria: (1) Patients with severe heart, liver and kidney insufficiency; (2) Patients with malignant tumors and other diseases; (3) Patients with brain trauma and other diseases.

All patients and their family members signed the informed consent form after being fully informed of the purpose and process of the study. This study was ratified by the ethics committee of our hospital and the ethics approval number was 2018-11-15. The two groups presented no significant disparity in general information (P>0.05). Table 1.

Methods

In group A, aripiprazole (Jiangsu Nhwa Pharmaceutical Co., Ltd, NMPA Approval Number H20140121) was adopted for the treatment with the initial dose of 10 mg per day, and the dose was gradually increased to a maximum of 30mg per day according to the patient's

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condition after continuous medication for one week. The course of treatment was 3 months.

In group B, olanzapine (Guangdong HEC Pharm Co., Ltd., NMPA Approval Number H20203493) was adopted for the treatment with the initial dose of 5mg per day and the dose was gradually increased to a maximum of 20 mg per day according to the patient's condition after continuous medication for one week. The course of treatment was 3 months.

In group C, risperidone (Xian Janssen Pharmaceutical Ltd., NMPA Approval Number H20010309, specification of 1mg) was adopted for the treatment with the initial dose of 5mg per day and the dose was gradually increased to a maximum of 15 mg per day according to the patient's condition after continuous medication for one week. The course of treatment was 3 months.

Observation indicators

The effective rate of the treatment courses for one, two, and three months was evaluated among three groups

The clinical efficacy was accessed by the PANSS score (Yinghuan *et al*., 2018). According to the scores, a reduction rate of 75% and above in the PANSS score indicated cured conditions, a reduction rate between 50% and 75% represented effective conditions and a reduction rate of less than 25% demonstrated ineffective conditions. PANSS score reduction rate = (Score before treatment - Score after treatment) / (Score before treatment - 30) × 100%. Effective rate = (Cured + Markedly effective + Effective) / Total cases × 100%.

PANSS and BEHAVE-AD scores of the three groups were evaluated.

Positive and Negative Syndrome Scale (Yaqing *et al*., 2018) includes positive symptoms, negative symptoms, and general pathological symptoms. The higher the score, the more serious the condition. BEHAVE-AD (Hongjuan *et al*., 2020) includes delusion, hallucination, behavior disorder, aggressive behavior, rhythm disorder, emotional disorder, anxiety and fear. A total score of 8 points and above is regarded as the upper limit. The higher the score, the more serious the pathological behavior.

Adverse reactions of the three groups were evaluated, including drowsiness, dizziness/headache, effects of extra pyramidal system (EPS), dry mouth and insomnia.

STATISTICAL ANALYSIS

SPSS 22.0 software was adopted to analyze the data. Measurement data were expressed with (x ± s) and analyzed by independent sample t-test/repeated test ANOVA; count data were expressed with (n%) and analyzed with χ^2/Fisher test or generalized estimation equation; P<0.05 was considered statistically significant.

RESULTS

Efficacy comparison

The results of GEE analysis showed that: in the term of groups, repeated measurement results described the values of Wald χ 2=0.283 and P=0.868.The effective rate of group A presented no statistical difference with group B and C with results of OR=e0.126=0.343 and 95% confidence interval of (e-0.672, e0.923) = (-1.827, 2.509). However, a statistical difference was revealed in terms of time points with Wald's χ 2=73.929 and P<0.001. For details, see tables 2 and 3.

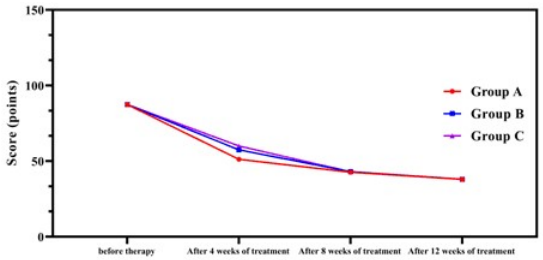

Figure 1 Comparison of PANSS scores in the three groups

Note: After 4 weeks of treatment, group B compared with group A, P<0.05; after 4 weeks of treatment, group C compared with group A, P<0.05.

Note: 4 weeks after treatment, a statistical difference of PANSS scores was detected between group A and group B (P<0.05) and also between group A and group C (P<0.05)

Fig. 1: PANSS scores comparison

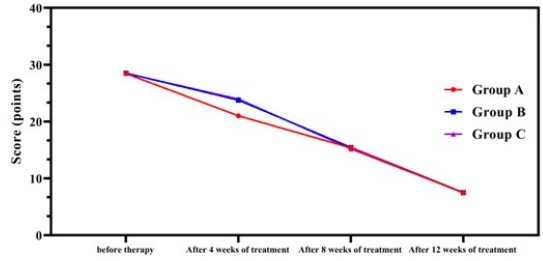

Figure 1 Comparison of PANSS scores in the three groups

Note: After 4 weeks of treatment, group B compared with group A, P<0.05; after 4 weeks of treatment, group C compared with group A, P<0.05.

Note: 4 weeks after treatment, a remarkable difference of Behave-AD scores was obtained between group A and group B (P<0.05) and also between group A and group C (P<0.05)

Fig. 2: Behave-AD scores comparison

PANSS score

Repeated measurement analysis of variance demonstrated that there were obvious differences in PANSS scores based on time points and cross-group comparison among the three groups (P<0.05), while there was no dramatical difference among the three groups (P>0.05). One-way analysis of variance illustrated that no statistical significance existed in PANSS scores among the three groups before treatment (P>0.05). After 4 weeks of treatment, the PANSS score of group A was significantly lower than that of groups B and group C (P<0.05). After 8 and 12 weeks of treatment, the three groups obtained similar PANSS scores (P>0.05). For details, see table 4 and fig. 1.

Table 1: Comparison of the general information between two groups

Group	Gender (n: %)		AVG. age (year)	AVG. course (year)	BMI (kg/m^2)
	Male	Female			
Group A (n=44)	23 (52.27)	21 (47.73)	70.45±5.32	5.62±2.32	22.78±2.32
Group B (n=42)	21 (50.00)	21 (50.00)	70.38±5.35	5.58±2.34	22.72±2.27
Group C (n=40)	19 (47.50)	21 (52.50)	70.42±5.27	5.60±2.29	22.75±2.29
χ^2/t	0.044		0.002	0.003	0.007
P	0.833		0.998	0.997	0.993

Table 2: Comparison of effective rate among three groups (n: %)

Group	n	Effective rate		
		1-month treatment	2-month treatment	3-month treatment
Group A	44	19 (43.18)	31 (70.45)	40 (90.91)
Group B	42	17 (40.48)	27 (64.29)	37 (88.10)
Group C	40	18 (45.00)	26 (65.00)	35 (87.50)
χ^2		Wald χ^2_{group}=0.283, Wald $\chi^2_{time\ point}$=73.929		
P		P_{group}=0.868, $P_{time\ point}$<0.001		

Table 3: Estimated parameters of GEE for the effective rate among three groups

Parameter	B	Standard error	95% Wald Confidence interval		Hypothesis test		
			Minimum limit	Maximum limit	Wald chi-square value	Freedom	Significance
(Intercept)	2.065	0.3838	1.313	2.818	28.959	1	<0.001
[Group=1.000]	0.126	0.4069	-0.672	0.923	0.096	1	0.757
[Group =2.000]	-0.081	0.4137	-0.892	0.730	0.039	1	0.844
[Group=3.000]	0	.	.	.	.	.	.
[Time point=1.000]	-2.371	0.2857	-2.931	-1.811	68.840	1	<0.001
[Time point=2.000]	-1.388	0.2502	-1.878	-0.898	30.781	1	<0.001
[Time point=3.000]	0	.	.	.	.	.	.
(Scale)	1						

Table 4: PANSS score comparison among three groups

Group	n	Before treatment	Treatment for 4 weeks	Treatment for 8 weeks	Treatment for 12 weeks
Group A	44	87.45±8.02	51.21±4.25$^{\#}$	42.71±2.32$^{\#}$	37.98±1.65$^{\#}$
Group B	42	87.39±7.92	57.45±5.45*$^{\#}$	43.05±2.25$^{\#}$	38.01±1.60$^{\#}$
Group C	40	87.42±8.05	60.05±5.68*$^{\#}$	42.95±2.34$^{\#}$	38.05±1.57$^{\#}$
F		$F_{time\ point}$=6459.214, $F_{cross\text{-}group}$=4.547, $F_{interaction}$=1.497			
P		$P_{time\ point}$<0.001, $P_{cross\text{-}group}$=0.012, $P_{interaction}$=0.228			

Table 5: BEHAVE-AD score comparison among three groups

Group	n	Before treatment	Treatment for 4 weeks	Treatment for 8 weeks	Treatment for 12 weeks
Group A	44	28.45±4.21	21.05±2.32$^{\#}$	15.21±1.25$^{\#}$	7.48±0.85$^{\#}$
Group B	42	28.51±4.17	23.78±3.21*$^{\#}$	15.45±2.85$^{\#}$	7.52±0.89$^{\#}$
Group C	40	28.47±4.23	23.81±3.28*$^{\#}$	15.35±2.34$^{\#}$	7.44±0.79$^{\#}$
F		$F_{time\ point}$=4370.010, $F_{cross\text{-}group}$=0.868, $F_{ineraction}$=1.497			
P		$P_{time\ point}$<0.001, $P_{cross\text{-}group}$=0.422, $P_{interaction}$=0.176			

Note: *P<0.05 in the comparison with group A and $^{\#}P$<0.05 in the comparison with the same group before treatment.

Table 6: Comparison of adverse reactions among three groups.

Group	Drowsiness	Dizziness/Headache	EPS	Dry mouth	Insomnia	Total incidence rate
Group A (n=44)	1 (2.27)	1 (2.27)	1 (2.27)	1 (2.27)	0 (0.00)	4 (9.09)
Group B (n=42)	3 (7.14)	4 (9.52)	2 (4.76)	1 (2.38)	2 (4.76)	12(28.57)*
Group C (n=40)	4 (10.00)	3 (7.5)	5 (12.5)	3 (7.50)	4 (10.00)	21 (52.50)*
Fisher/χ^2	Fisher	Fisher	Fisher	Fisher	Fisher	5.385
P	0.312	0.351	0.147	0.445	0.063	0.020

Note: *P<0.05 in the comparison with group A

BEHAVE-AD score comparison

Repeated measurement analysis of variance discovered that a marked difference in the time point of the BEHAVE-AD score among the three groups (P<0.05), but there was no significant difference in the cross-group comparison and interaction comparison (P>0.05). One-way analysis of variance manifested no great disparity in the BEHAVE-AD score before treatment among the three groups (P>0.05). After 4 weeks of treatment, the BEHAVE-AD score in group A was inferior to that in groups B and group C (P<0.05). After 8 and 12 weeks of treatment, there was no substantial difference in the score of BEHAVE-AD between group A and groups B and C (P>0.05). For details, see table 5 and fig. 2.

Comparison of adverse reactions

Group A obtained a markedly lower total incidence rate of adverse reactions than in group B and C (P<0.05) (see table 6)

DISCUSSION

Senile dementia is a common clinical disease in which vascular dementia and Alzheimer's disease are the most common. Epidemiological investigation concluded (Xingrong, 2020) an approximate AD incidence rate of ten percent in the elderly population and an estimation of more than four million AD patients in China. Age has been confirmed (Cheng *et al*., 2019) to be a risk factor for AD. The incidence rate of AD increases with age especially with an age over 90-year-old, as aging gives rise to vascular sclerosis, cerebral insufficiency and degenerative changes in the body, such as the downward ability to eliminate harmful substances, which will aggravate the damage to the nervous system. In addition, the deficiency of activities and exercises in the elderly may result in a propensity for a cascade of chronic diseases, which nessecitates the implementation of effective treatment to control the development of the disease.

Currently, atypical antipsychotics such as olanzapine and aripiprazole are widely used in the treatment of AD. Olanzapine is a receptor antagonist of 5-hydroxytryptamine (5-HT) and dopamine (DA). Its strong affinity for 5-HT, DA, α-adrenaline, and histamine H can block D2 receptor and 5-HT in limbic system, inhibit dopamine desaturation, and reduce the release of Da (Junfei *et al*., 2019; Mingqiu and Hanjun, 2018). Moreover, it can selectively act on the limbic system of midbrain, affect cholinergic nervous system, and inhibit the decrease of cholinergic neurons to enhance the positive symptoms of AD patients (Mukhopadhyay *et al*., 2017). Aripiprazole is a D2 receptor subtype 2 (D2 receptor) and 5-HT1A receptor agonist. A study (Yanxin *et al*., 2018) found that it has a bi-directory regulation effect on the dopaminergic nervous system, and can produce anti positive symptoms by activating D2 and 5-HT1A receptors and antagonizing 5-HT2A receptors. In addition, this kind of drug can suppress the upregulation of DA neurons in an excited state to a certain extent and enhance the cognitive function of patients. Risperidone drug, a derivative of promethazine isoxazole, has also been recommended for treatment by several studies. It has strong affinity with dopamine D2 and 5-HT2A receptors, low affinity with H1 histaminergic and α-adrenergic receptors and no affinity with cholinergic receptors, which can promote the release of dopamine by blocking 5-HT2A receptors to modify the negative symptoms and cognitive symptoms (Junwei *et al*., 2018; Xue *et al*., 2018; Yu *et al*., 2018). The results of this study showed that there was no significant difference in the effective rateamong the three groups, suggesting that olanzapine, aripiprazole and risperidone can improve the neurobehavioral symptoms of Alzheimer's disease. However, after 4 weeks of treatment, the group A had lower PANSS scores and Behave-AD scores than group B and group C, which may be attributed to its rapid efficacy in treatment.

Notwithstanding the similar efficacy of the three drugs, they differ greatly in terms of safety, especially risperidone. Due to its long half-life period, the plasma concentration of risperidone in patients with Alzheimer's disease will increase with the increase of dosage. Nonetheless, given the degenerative changes and slow metabolism of the elderly, patients are predisposed to adverse reactions (Ying *et al*., 2017). Aripiprazole, with a relatively short half-life period and little effect on the metabolism of patients, can ameliorate the drug resistance of patients, which may stem from the inhibitory effect of aripiprazole on the activity of serotonergic nerve of substantia nigra striatum pathway quotient, accompanied by a bi-directory regulation effect on dopaminergic nerve, reducing the adverse reactions when dopamine D2 receptor is antagonistic. Therefore, aripiprazole is more suitable for senile dementia patients. In the adverse reactions, group A obtained a significantly lower total incidence rate compared with that of groups B and group C, which was consistent with the research results of Zhang Zhihong *et al*. (Zhihong and Zhibin, 2018) and Chen Peidong *et al*. (Dong and Liqin, 2017), indicating the safety profile of aripiprazole.

CONCLUSION

In summary, aripiprazole, olanzapine and risperidone can improve behavior disorder and cognitive function, in which aripiprazole with a better safety profile, is more suitable for elderly patients.

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