•Original article•

Relationship of changes in cognitive and depressive symptoms during antidepressant treatment of individuals with geriatric depression and their relationship to the APOE epsilon 4 allele

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Background: Co-occurring cognitive impairment in geriatric depression may not improve with antidepressant treatment and it may progress to dementia.

Aim: Assess the relationship between changes in cognitive and depressive symptoms among patients with geriatric depression and their association with the APOE epsilon 4 allele before and after antidepressant treatment.

Methods: The presence of the APOE epsilon 4 allele was assessed in 64 incident cases of geriatric depression and 31 elderly individuals without depression and the Geriatric Depression Scale (GDS), Mini-Mental State Examination (MMSE), digit span test, and Trail Making Tests A and B (TMT-A, TMT-B) were administered to these subjects at baseline and 12 months after baseline, during which time the depressed group received standardized treatment with selective serotonin reuptake inhibitors (SSRIs).

Results: Prior to treatment patients with geriatric depression had significantly worse cognitive functioning than control subjects and 31 (48%) met criteria for mild cognitive impairment (MCI). After treatment depressed patients with and without comorbid MCI both had significant improvements in their depressive and cognitive symptoms, but those with MCI had more residual symptoms. The severity of cognitive symptoms was not associated with the severity of depressive symptoms at baseline, but they were positively correlated at the 12-month follow-up. The APOE epsilon 4 allele was identified in 14% (9/64) of the patients and in 3% (1/31) of the controls (Fisher's Exact Test, p=0.158). Compared to depressed patients without the allele, depressed patients with the allele had more severe cognitive deficits both before and after treatment, though only some of these differences were statistically significant.

Conclusions: There is substantial cognitive impairment in elderly individuals with geriatric depression. Both the depressive and cognitive symptoms improve with standard SSRI treatment, but individuals with comorbid MCI have more residual depressive and cognitive symptoms after treatment. The APOE epsilon 4 allele is associated with greater cognitive impairment in geriatric depressed patients and may be associated with less responsiveness of cognitive symptoms to antidepressant treatment.

1. Introduction

Cognitive impairment is common in geriatric depression.[1,2] Some authors suggest that the cognitive impairment in geriatric depression does not improve with remission of depression, and it may even progress to fully-blown dementia.[3] One rationale for such a relationship is that Alzheimer's Disease and late-onset depression share a common genetic risk factor, the epsilon 4 allele of the apolipoprotein E gene (APOE).[4,5] It remains unclear if the cognitive impairment seen in some geriatric patients with depression is independent of depressive symptoms, one of the symptoms of the depressive episode, or both. We hypothesize that the cognitive impairment seen in patients with geriatric depression persists after depressive symptoms resolve, particularly in those with the epsilon 4 allele of APOE. To assess this hypothesis we classified elderly individuals with a first episode of depression into those with and

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without co-occurring mild cognitive impairment (MCI) and then followed the one-year trajectory of cognitive and depressive symptoms in these patients as they received antidepressant treatment for their depression.

2. Methods

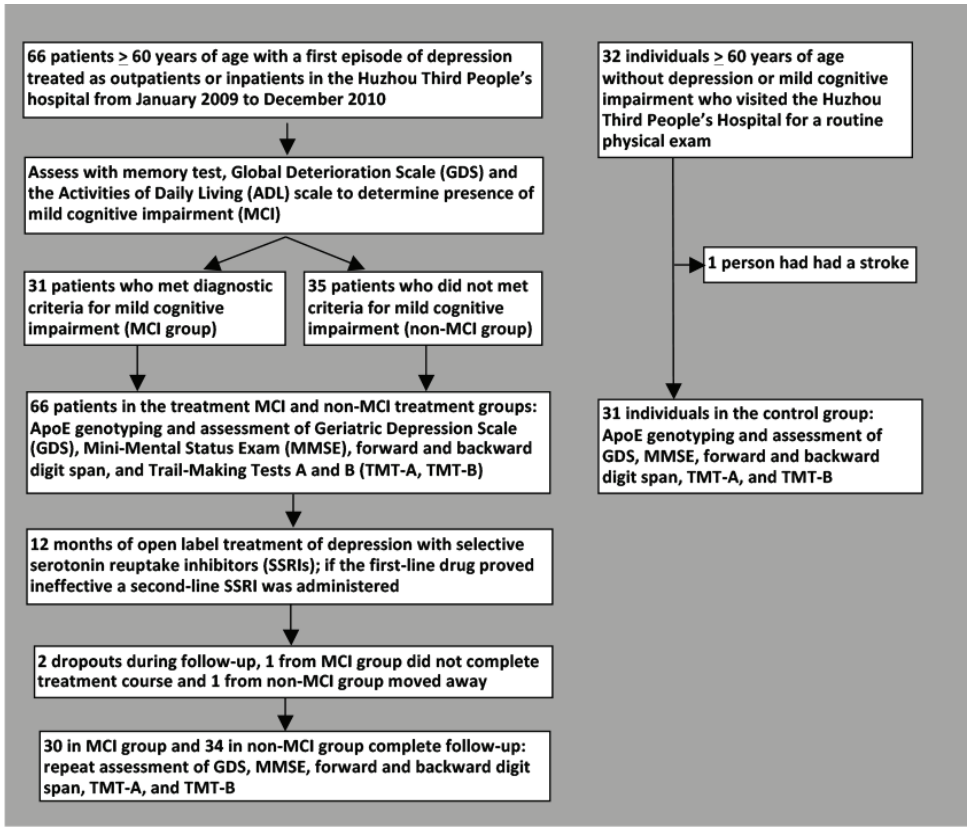
2.1 Sample identification

The flowchart for the study is shown in Figure 1. This is a prospective study of patients with first-onset geriatric depression who sought outpatient or inpatient treatment at the Third People's Hospital of Huzhou from January 2009 to December 2010. Included patients were at least 60 years of age, met diagnostic criteria for depression specified in the *3rd edition of the Chinese Classification of Mental Disorders* (CCMD-3),[6] had a score of at least 11 on the Geriatric Depression Scale (GDS),[7] had had no prior episode of depression, had no history of alcohol or drug dependence, had no serious medical condition (including neurodegenerative disorders, cerebrovascular disease, or serious diseases of the heart, liver or kidney) and signed a consent form to participate in the study. The 64 enrolled patients who completed the 12-month follow-up included 17 males and 47 females with a mean age of 67.5 (s.d.=6.0) years and a mean duration of education of 8.9 (4.2) years.

The criteria proposed by Petersen[8] were used to identify depressed patients with MCI: (a) impaired memory reported by the patient or their relatives; (b) a memory test score of at least 1.5 standard deviations lower than normal controls with the same age and educational level; (c) a grade of 2 to 3 in the Global Deterioration Scale (GDS)[9]; (d) normal general cognitive functioning and daily functioning with an Activity of Daily Living (ADL)[8] score lower than 26; and (e) no diagnosis of dementia or any other physical or mental illness that may lead to brain dysfunction. Among the 64 patients with geriatric depression who completed the 12-month follow-up, 30 (46.9%) met these criteria for MCI.

Control subjects were recruited from patients 60 years or older seeking a routine physical examination at the Geriatric Department or the Physical Examination Center of the Third People's Hospital of Huzhou. Individuals with a serious physical illness, those who met the above criteria for depression or MCI and those with a family history of depression, dementia or MCI in first-degree relatives were excluded. The 31 recruited controls, all of whom signed consent forms, included 13 males and 18 females, had a mean age of 68.2 (8.6) years and a mean duration of education of

Figue 1. Flowchart for the study



9.0 (4.0) years. There were no statistically significant differences between patients and controls in age (t=-0.415, p=0.687), gender (χ^2=2.28, p=0.131), or years of education (t=-1.09, p=0.280).

2.2 Assessment and treatment

Study participants were administered the GDS, the Mini-Mental State Exam (MMSE),[10] the forward and backward digit span task, and the Trail-Making Tests A and B (TMT-A, TMT-B)[11] at baseline and the patient group was re-administered these tests after 12 months of treatment with antidepressant medication. All tests were independently administered by two senior attending doctors. Their inter-rater reliability for the various scales was good; the intraclass coefficient (ICC) for MMSE was 0.84, that for the digit span tests was 0.85, that for the TMT-A and TMT-B tests was 0.85, and that for the GDS was 0.88.

In the morning of the day of enrolment, two milliliters of blood was drawn from all participants. These samples were stored at -80 °C and the TIANamp Genomic DNA Kit (DP304) was used for DNA extraction to identify the epsilon 4 isoform of the APOE gene. The TaKaRa LA Taq with GC Buffer (DRR02AG) and BIO-RAD MJ Mini Opticon Real-Time Polymerase Chain Reaction (PCR) System was used for the extraction, the PCR primer was made by Invitrogen (Shanghai), and the PCR sequencing was completed by the Shanghai Majorbio Bio-Pharm Technology Company.

The depressed patients were treated according to the Treatment and Prevention Guidelines for Depressive Disorder of China (issued by the Chinese Medical Association in 2006).[12] All patients were treated with selective serotonin reuptake inhibitors (SSRIs) at adequate dosages for sufficient time. After initial titration of the dosage, the dosages remained stable throughout the acute, continuation and maintenance phases of treatment. The first choice of SSRI was not effective after 6 weeks of treatment (i.e., decrease in GDS <50%) in 19 of the 64 (29.7%) patients so they were converted to a different SSRI; 9 of these patients (14.1%) had still not improved at the end of the 12 months of follow-up. The first line medications used were sertraline (50 to 150 mg/d) or citalopram (20 to 60 mg/d) and the second-line medication was paroxetine (20 to 40 mg/d). After 12 months most patients had completed their full course of antidepressant treatment, only 21 of the 64 patients (32.8%) were still using antidepressant medication at the 12-month follow-up.

This study was approved by the ethical review committee of the Third Hospital of Huzhou.

2.3 Statistical analysis

All analyses were conducted using SPSS (version 17.0) software. Chi-squared test, t-test, repeated measures ANOVA, and Spearman correlation coefficients were used for data analysis. All tests were two-tailed and statistical significance was set as p<0.05.

3. Results

3.1 Comparison of cognitive functioning at baseline

As shown in Table 1, compared to the control subjects the depressed patients had significantly lower total scores on the MMSE, shorter digit spans and took longer to compete the trail making tests. Thus, the depressed patients were more cognitively impaired than control subjects of the same age and gender.

3.2 Comparison of depressive symptoms and cognitive functioning in depressed elderly with and without MCI before and after treatment

As shown in Table 2, the severity of depression at baseline was not statistically different between elderly depressed subjects with and without concurrent MCI.

Table 1. Comparison of cognition functioning between 64 patients with geriatric depression and 31 controls at baseline (mean [SD])

	Mini Mental Status Exam (score)	Digit Span Tasks (number)			Trail-Making Tests (seconds)	
		Forward	Backward	total	A	B[a]
Patients	28.0(2.2)	7.4 (1.3)	4.6 (1.0)	12.0 (1.9)	71.5 (20.9)	127.2 (44.9)
Controls	29.9(0.3)	8.4 (1.0)	6.7 (1.2)	15.0 (1.6)	54.4 (16.0)	85.3(27.2)
t-value	-6.87	-3.89	-8.95	-7.63	4.47	4.62
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[a] The TMT-B test was completed by 48 patients and 23 controls

After 12 months of treatment for depression the severity of depression improved significantly in both types of patients but those with concurrent MCI at baseline had significantly more residual symptoms of depression after 12 months of treatment than patients who did not have concurrent MCI at baseline. The magnitude of the change in the before versus after GDS score was smaller in the MCI group, but this difference did not reach statistical significance (p=0.065).

With the exception of the TMT-A test, all of the cognitive measures assessed showed significantly greater impairment in the MCI group at baseline and these differences persisted after 12 months of treatment for depression. In most cases the individual cognitive tests improved over the 12 months in both the MCI group and the non-MCI group, but the improvement in the backward digit span for the MCI group did not reach statistical significance, the improvement in the forward digit span for the non-MCI group did not reach statistical significance, and the total MMSE score in the non-MCI group showed a non-significant decrease over the 12 months. The improvement in the MMSE score over the 12 months was significantly greater in the MCI group than in the non-MCI group, but there were no significant differences in the magnitude of the improvement between the two groups in any of the other cognitive measures.

3.3 Correlation between severity of depression and cognitive functioning before and after treatment

As shown in Table 3, prior to treatment the severity of depression was only weakly correlated with the severity of cognitive impairment as measured by the different scales. Twelve months after initiating antidepressant therapy the residual level of depressive symptoms was significantly associated with the severity of three of the five cognitive measures (MMSE, forward digit span and backward digit span).

3.4 Prevalence of epsilon 4 allele of the APOE genotype and its relationship to the severity of depression and cognitive functioning before and after treatment in depressed subjects

Among the depressed patients 14.1% (9/64) had the epsilon 4 allele of the APOE genotype but only 3.3% (1/30) of the control subjects had this allele (Fisher's Exact Test, p=0.158). Table 4 compares the depressive and cognitive symptoms between the 9 patients with geriatric depression who had the epsilon 4 allele and the 55 patients who did not have the allele. At baseline and at the 12 month follow-up the severity of depressive symptoms between those with and without the APOE epsilon 4 allele was similar. Both types of patients showed significant improvements in depressive symptoms with treatment; the magnitude of improvement was slightly greater in those without the allele but this difference was non-significant (p=0.164).

At baseline the MMSE and digit span tests results were not significantly different between those with and without the APOE epsilon 4 allele, but those with the allele took significantly longer to complete the TMT-A and TMT-B tests. At the 12-month follow-up all cognitive tests improved in the depressed patients who did not have the APOE epsilon 4 allele, but in the subgroup with the epsilon 4 allele only the two trail-making tests showed significant improvement; the two digit span tests in those with the epsilon 4 allele showed non-significant improvement and the MMSE showed non-significant deterioration. At the end of the 12 months the MMSE score, the backward digit test and the TMT-A test were significantly worse in the subgroup with the epsilon 4 allele than in the subgroup without the allele. The magnitude of improvement in the MMSE score over the 12 months was significantly greater in those without the allele, but there were no significant differences in the magnitude of improvement between

Table 2. Comparison of the depressive and cognitive measures between elderly depressed patients with and without mild cognitive impairment (MCI) at baseline and 12 months after initiating treatment for depression (mean [SD])

	Baseline assessment				12-month follow-up				Before v. after change score			
	with MCI (n=30)	without MCI (n=34)	t value	p value	with MCI (n=30)	without MCI (n=34)	t value	p value	with MCI (n=30)	without MCI (n=34)	t value	p value
Geriatric Depression Scale	20.6 (2.6)	20.6 (2.5)	0.07	0.944	9.5 (3.3)[a]	7.7 (3.4)[a]	2.15	0.035	11.2 (4.2)	12.9 (3.4)	-1.88	0.065
Mini-Mental Status Exam	25.8 (1.1)	29.9 (0.2)	-19.75	<0.001	27.6 (3.1)[a]	29.1 (1.5)	-2.42	0.020	1.7 (3.1)	-0.9 (1.4)	4.40	<0.001
Forward digit span	6.8 (1.1)	7.9 (1.2)	-3.90	<0.001	7.6 (1.0)[a]	8.2 (1.0)	-2.59	0.012	0.8 (1.2)	0.3 (1.0)	1.88	0.065
Backward digit span	4.1 (1.0)	5.0 (0.8)	-4.07	<0.001	4.9 (1.1)	6.1 (1.2)[a]	-4.10	<0.001	0.9 (1.0)	1.1 (1.5)	-0.70	0.488
Trail-Making Test-A	71.3 (18.8)	71.8 (17.9)	-0.11	0.914	56.4 (14.3)[a]	52.6 (14.8)[a]	1.04	0.305	14.9 (15.6)	19.2 (15.9)	-1.08	0.282
Trail-Making Test-B	133.4 (42.7)	109.0 (37.0)	2.46	0.017	103.9 (28.5)[a]	91.5 (14.8)[a]	2.23	0.029	29.4 (32.0)	17.5 (26.7)	1.63	0.109

[a] Statistically significant difference between the baseline and the 12 month follow-up result using repeated measure ANOVA, p<0.01

Table 3. Correlation of cognitive measures with severity of depression (using Geriatric Depression Scale score) among 64 patients with geriatric depression at baseline and 12 months after initiating treatment for depression

		Mini Mental Status Exam	Digit Span		Trail Making Test	
			Forward	Backward	TMT-A	TMT-B
Baseline	r	-0.10	-0.24	-0.11	0.16	0.16
	p	0.419	0.058	0.374	0.202	0.220
12-month follow-up	r	-0.47	-0.26	-0.38	0.20	0.15
	p	<0.001	0.039	0.002	0.107	0.247
Before v. after change in score (improvement)	r	0.20	0.05	0.18	0.15	-0.08
	p	0.121	0.675	0.166	0.239	0.544

the two subgroups for any of the other cognitive measures.

4 Discussion

4.1 Main findings

We found that patients who meet criteria for geriatric depression have substantial impairments in their cognitive functioning as assessed by the MMSE, digit span tasks and the Trail-Making tests. Using the criteria specified by Peterson[8] 48% of them (31/64) met criteria for MCI. These findings are similar to those of other studies that find impairments in memory and executive function in elderly individuals with depression,[13,14] which may be related structural and functional impairments in the hippocampus in persons with depression.[15]

We also found that both depressive and cognitive symptoms of elderly individuals with depression improve with standardized treatment for depression with SSRIs. Thus our initial hypothesis that cognitive symptoms in depressed elderly get worse and may progress to full-criteria dementia during antidepressant treatment was not supported, at least for the first year after initiation of antidepressant treatment. When subdividing the depressed group into those with and without MCI at baseline, there were more residual depressive and cognitive symptoms in the MCI group than in the non-MCI group after treatment, but the magnitude of the before-versus-after improvement in the MMSE score (the most comprehensive measure of cognitive functioning used in the study) was actually greater in the MCI group. This suggests that the cognitive symptoms in depressed elderly have both trait (i.e., long-lasting symptoms that may be markers of subsequent dementia) and state (i.e., symptoms that are amenable to treatment) components. Our findings are similar to those of Yuan and colleagues[16] who report that the responsiveness of depressive symptoms to antidepressant treatment is less marked in depressed elderly with prominent cognitive symptoms, and to those of Zhang and colleagues[17] who report partial improvement of cognitive symptoms in depressed elderly during antidepressant treatment. A study by Butters and colleagues[18] also found partial

Table 4. Comparison of the depressive and cognitive measures between elderly depressed patients with and without the ApoE4 genotype (mean [SD])

	Baseline assessment				12-month follow-up				Before v. after change score			
	with ApoE4 (*n*=9)	without ApoE4 (*n*=55)	t value	p value	with ApoE4 (*n*=9)	without ApoE4 (*n*=55)	t value	p value	with ApoE4 (*n*=9)	without ApoE4 (*n*=55)	t value	p value
Geriatric Depression Scale	19.2 (2.6)	20.8 (2.3)	0.672	0.504	8.8 (2.1)[a]	8.5 (3.7)[a]	-0.26	0.798	10.4 (3.6)	12.4 (3.9)	1.41	0.164
Mini-Mental Status Exam	27.6 (1.9)	28.1 (2.3)	1.82	0.074	26.0 (4.2)	28.8 (1.9)[a]	3.33	0.001	-1.6 (3.9)	0.7 (2.4)	2.36	0.021
Forward digit span	7.0 (0.9)	7.5 (1.3)	1.39	0.186	7.4 (0.7)	8.0 (1.0)[a]	1.58	0.119	0.4 (1.0)	0.6 (1.1)	0.25	0.800
Backward digit span	4.1 (1.5)	4.6 (0.9)	1.05	0.321	4.3 (1.2)	5.8 (1.2)[a]	3.37	0.001	0.2 (1.1)	1.1 (1.3)	1.95	0.055
Trail-Making Test-A	84.4 (7.6)	69.4 (18.6)	-2.38	0.020	61.3 (8.3)[a]	53.2 (15.1)[a]	-2.36	0.030	23.1 (13.7)	16.2 (16.0)	-1.22	0.226
Trail-Making Test-B	155.0 (49.4)	114.8 (37.4)	-2.86	0.006	109.8 (25.2)[a]	95.3(22.2)[a]	-1.78	0.079	45.2 (49.3)	19.5 (23.9)	-1.54	0.160

[a] Statistically significant difference between the baseline and the 12 month follow-up result using repeated measure ANOVA, $p<0.01$

improvement in the comorbid cognitive symptoms of depressed elderly; but their study suggested that problems with executive functioning in these patients were more likely to be treatment resistant, a finding that we did not confirm.

The patients with geriatric depression were more likely to have the APOE epsilon 4 allele than individuals in the control group (a non-significant difference), but there were only 9 patients with the allele so our results must be considered preliminary, needing confirmation in larger samples that have more patients with the APOE epsilon 4 allele. Our results suggest that some cognitive functions are more severely impaired in depressed elderly who have the epsilon 4 allele than in depressed elderly without the allele both before and after antidepressant treatment. Moreover, the MMSE score in patients with the APOE epsilon 4 allele decreased over the year of treatment while the corresponding score in patients without the allele increased. The APOE epsilon 4 allele is considered a predisposing gene for sporadic AD,[5] so the presence of this allele in individuals with geriatric depression may mean that more of the comorbid cognitive symptoms are 'trait' symptoms that are not amenable to antidepressant treatment

4.2 Limitations

The patients identified in this study were those who came to a psychiatric outpatient center for treatment, so they were probably more severely depressed than most elderly depressed individuals in the community. We only used a small number of cognitive tests and did not conduct neuroimaging tests so we were limited in our ability to interpret the underlying pathophysiology related to our findings. Most of the depressed patients had completed their course of treatment at the time of the 12-month follow-up so the post-treatment results combined those of patients who were and were not currently taking antidepressants. The sample size was sufficient to compare cognitive measures between depressed patients and normal controls, and to compare depressive symptoms and cognitive functioning before and after treatment in the depressed patients, but the analyses comparing the outcomes for depressed patients who did and did not have MCI and for patients who did and did not have the APOE epsilon 4 allele was inconclusive because of the small number of depressed patients in the subgroups. The analyses comparing these subgroups in which there were significant differences are valid, but the analyses in which there were non-significant differences between subgroups may have been due to Type II errors.

4.3 Significance

Individuals who meet criteria for geriatric depression treated in outpatient psychiatric clinics in China have substantial cognitive deficits compared to elderly controls without depression; almost one-half of these individuals met criteria for mild cognitive impairment (MCI). The severity of depression in depressed geriatric patients with and without comorbid MCI are similar before treatment and both subgroups of patients improve significantly with antidepressant treatment, but those with comorbid MCI have more residual depressive symptoms at the end of treatment. The cognitive symptoms in both groups also improve during treatment for depression; in most cases the improvement in cognitive symptoms is greater in the patients with comorbid MCI but at the end of one year patients who had MCI at baseline still have significantly greater cognitive deficits than those who did not have MCI at baseline.

Only 9 of the depressed elderly patients in this study had the APOE epsilon allele so it is not possible to come to any definitive conclusions about its role in depression and dementia. Nevertheless, despite depressive symptoms of similar severity in patients with and without the APOE epsilon allele, several of the cognitive measures assessed were significantly worse in patients with the allele both before and after antidepressant treatment and the magnitude of improvement in the MMSE (the main measure of cognitive functioning) with treatment was significantly smaller in those with the allele.

Conflict of Interest

The authors report not conflict of interest related to this manuscript.

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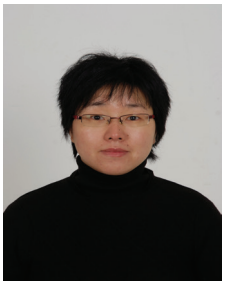

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•论著•

老年抑郁症患者抗抑郁药治疗期间认知与抑郁症状的变化及其与ApoEε4等位基因的关系

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摘要

背景 老年抑郁症伴有的认知损害可能不随抗抑郁治疗而好转，可能会进展为痴呆。

目的 探讨老年抑郁症患者抗抑郁治疗前后认知和抑郁症状变化的关系及其与ApoEε4等位基因的关联。

方法 检测64例首发老年抑郁症患者和31名非抑郁老年人的ApoEε4等位基因。抑郁症患者接受标准化的选择性5-羟色胺再摄取抑制剂（Selective Serotonin Reuptake Inhibitors, SSRIs）治疗，在基线和治疗12个月后分别对研究对象进行老年抑郁量表(The Geriatric Depression Scal, GDS)、简易智能状态检查（Mini-Mental State Examination, MMSE）、数字广度测验（digit span task）和连线测验A, B（Trail making test, TMT-A, TMT-B)的测评。

结果 与对照组比较，治疗前老年抑郁症组患者的认知功能较差，其中31（48%）例符合轻度认知功能损害（mild cognitive impairment, MCI）的标准。治疗后，无论共病MCI与否，抑郁症患者的认知和抑郁症状均有改善，但伴MCI者残留症状更多。基线时认知症状的严重程度与抑郁症状的严重程度不存在相关性，但在12个月随访时二者存在正相关。患者中有14%（9/ 64）携带ApoEε4等位基因，而对照中仅有3%（1/31）携带APOEe4等位基因（Fisher精确检验，p=0.158）。与未携带ApoEε4等位基因的抑郁症患者相比，携带此等位基因的抑郁症患者治疗前、后均有较严重的认知症状，但仅某些方面的差异具有统计学意义。

结论 老年抑郁症患者普遍存在认知损害。经标准的SSRI治疗后，患者的抑郁和认知症状均有所改善，但共病MCI的患者治疗后残留更多的抑郁和认知症状。老年抑郁症患者中携带ApoEε4等位基因与较严重的认知损害有关，可能与抗抑郁剂治疗认知症状疗效欠佳有关。