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Therapeutic effects of the selective serotonin noradrenaline reuptake inhibitor milnacipran on depressive symptoms in patients with Alzheimer's disease

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ABSTRACT

To clarify the profile of depressive symptoms in major depressive episodes in patients with Alzheimer's disease (AD-MD), we compared AD-MD with major depressive disorder in non-demented elderly patients (MDD) matched for age, using the 17-item Hamilton Rating Scale for Depression (HAM-D_{17}). In addition, to clarify which depressive symptoms of AD patients respond to treatment with the selective serotonin and noradrenaline reuptake inhibitor (SNRI) milnacipran, we compared the HAM-D_{17} average score and the score of each HAM-D item, the mini-mental state examination (MMSE) score, and GAF score according to the DSM-IV evaluation of AD-MD patients at baseline and at the endpoint (12 weeks).

Depressive mood, loss of interest in hobbies and social activities and anxiety (psychic) scored the highest in both AD-MD and MDD groups, while psychomotor retardation scored significantly higher in AD-MD, and insomnia and anxiety (somatic) significantly did so in MDD. We also found that depressive mood, suicidal tendency, loss of interest, psychomotor retardation, anxiety (psychic), gastrointestinal symptoms, general somatic symptoms, and hypochondriasis remarkably improved in patients of AD-MD treated with milnacipran.

Our results suggest that in general the profiles of depression in AD-MD and MDD are similar, despite some different clinical features between both conditions. Our study also suggests that milnacipran is *promising* to treat a broad range of depressive symptoms in AD-MD patients.

1. Introduction

One of the peculiar clinical features of depressive state in elderly people is the association with dementia, such as Alzheimer's disease (AD). It is documented that around one fourth of patients with AD experience major depressive episodes (Burns et al., 1990; Migliorelli et al., 1994), which have an immense impact on the quality of life of AD patients (Gonzales-Salvdor et al., 2000). However, thus far, there have been very few studies focusing on the clinical features of major depressive symptoms in patients with AD (AD-MD), and clinical features of AD-MD are still unclear.

In the treatment for AD-MD, it is well known that the anticholinergic effect of antidepressants on cognitive function is critical (Teri et al., 1991), thus selective serotonin reuptake inhibitors (SSRIs) may be effective (Katz, 1998). However, there have been few studies on the effectiveness of SSRIs (Burke et al., 1997; Taragano et al., 1997; Magai et al., 2000; Petracca et al., 2001; Lyketsos et al., 2003), and their results are inconsistent. In addition, despite a relative low prevalence of side effects associated with SSRIs, these drugs are sometimes intolerable for older people since they experience nausea, vomiting, dizziness and drowsiness (Wilson and Mottram, 2004). In addition, SSRIs are metabolized via the cytochrome P450 system and inhibit isoenzymes, which involve the risk of adverse effects due to drug interactions. Thus, it is important to develop other effective and safe drugs for AD-MD.

Milnacipran is a selective serotonin and noradrenaline reuptake inhibitor (SNRI) (Puech et al., 1997) that is devoid of any postsynaptic activity (Moret et al., 1985). Furthermore, milnacipran has metabolic advantages over SSRIs, because it does not inhibit any cytochrome P450 isoenzymes (Puozzo and Leonard, 1996), reducing thereby the risk of adverse effects due to drug interactions, compared to SSRIs. Accordingly, SNRI should be an important antidepressant for patients with AD-MD, although thus far we have carried out the only study that showed effectiveness of milnacipran in such patients (Mizukami et al.,

Abbreviations: AD, Alzheimer's disease; AD-MD, Major depressive episodes in patients with Alzheimer's disease; BRSD, Behavior rating scale for dementia; CDR, Clinical dementia rating; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; FAST, Functional assessment staging; HAM-D_{17}, The 17-item Hamilton Rating Scale for Depression; MDD, Major depressive disorder; MMSE, Mini-mental state examination; NINCDS/ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; SNRI, Selective serotonin and noradrenaline reuptake inhibitor; SSRI, Selective serotonin reuptake inhibitors.

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Table 1
Demographic data of 14 patients with AD and major depressive episodes (AD-MD) and 22 non-AD elderly patients with major depressive disorder (MDD)

	AD	Non-AD	
No. of subjects	14	22	
Sex			
Female	10	14	$p=0.9038$ (χ^2 test)
Male	4	8	
Mean age	74.3±10.1	71.9±5.8	$p=0.3742$ (t test)
~60's	4	9	$p=0.3010$ (χ^2 test)
70's	6	11	
80's	4	2	
HAM-D score	18.0±3.6	20.8±5.7	$p=0.1083$ (t test)
10–19	9	9	$p=0.3306$ (χ^2 test)
20–29	5	12	
30–	0	1	
GAF score	34.1±12.3	49.6±7.6	$p<0.0001$ (t test)

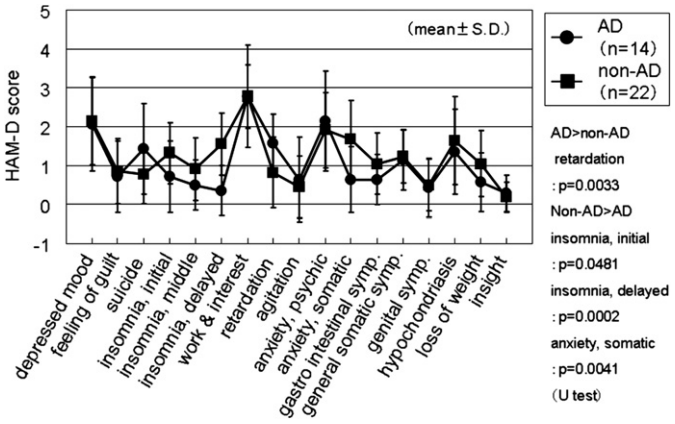

Fig. 1. HAM-D_{17} scores of AD-MD and MDD patients.

2006). Nevertheless, the effectiveness and safety of SNRI remain to be clarified.

Thus, the first objective of this study is to clarify the profile of the depressive state in AD-MD and compare the clinical features between AD-MD and major depressive disorder (MDD) in elderly patients matched for age. The second objective of this paper is to clarify which depressive symptoms of AD patients respond to treatment with milnacipran.

2. Materials and methods

2.1. Patients

Fourteen consecutive patients (75.2±9.4 years old) were enrolled in this study; all of them were recruited from the outpatient clinic of Ishizaki Hospital, and patients themselves or their care providers gave their written informed consent to participate in the study. This study protocol was approved by the Internal Review Board of Ishizaki Hospital, and was carried out in accordance with the ethics and principles embodied in the 1975 Declaration of Helsinki. AD was clinically diagnosed based on DSM-IV (American Psychiatric Association, 1994) and NINCDS/ADRDA (McKhann et al., 1984) criteria. In addition, all 14 patients fulfilled the DSM-IV criteria for major depressive episode, and their HAM-D_{17} (Hamilton, 1960) scores were greater than 12. The subjects for the clinical dementia rating (CDR) (Hughes et al., 1982) 1 and CDR 2 were 8 and 6, respectively, and those for functional assessment staging (FAST) (Reisberg, 1988) 4, 5, and 6 stages were 10, 3, and 1, respectively. One of the 14 patients (Case 3) had a past history of major depressive episodes. We compared the HAM-D_{17} data of the 14 AD-MD patients with those from 22 MDD patients. Demographic data of the 14 AD-MD and 22 MDD patients are given in Tables 1 and 2.

The protocol was as previously described (Mizukami et al., 2006). AD-MD patients were started on milnacipran at 15 mg or 30 mg daily. If a patient showed no improvement within 2 weeks, the dose was increased every 2 weeks by 15 mg/day increments. Case 3 received antidepressants, such as sulpiride and mianserin, and 10 patients received antidementia drugs. The dose of these concomitant drugs was unchanged during the treatment of milnacipran. The HAM-D_{17} average score and the score of each HAM-D item, the mini-mental state examination (MMSE) score (Folstein et al., 1975), and GAF score according to the DSM-IV of AD-MD patients at baseline and at the endpoint (at 12 weeks) were compared. If patients discontinued milnacipran before 12 weeks, the week of discontinuation was defined as the endpoint.

Statistical analysis was carried out using the χ^2 test to examine the differences in sex, age, and HAM-D score between AD-MD and MDD groups. Student's t-test was also used to detect differences in age, HAM-D score, and GAF score between the two groups. Mann–Whitney's U test was used to detect differences in the score of each HAM-D item between the two groups. Wilcoxon method was used to examine differences in the score of each HAM-D item of AD-MD patients between at baseline and at the endpoint. Differences with a p value of <0.05 were regarded as statistically significant.

3. Results

The average HAM-D_{17}, MMSE and GAF scores of the 14 AD-MD patients at baseline were 18.0±3.6 (range 12–24), 19.3±4.1 (range 9–25),

Table 2
Summary of clinical data from 14 patients

No	Age	Sex	CDR	FAST	No. of depressive episode	Concomitant antidepressants	Concomitant antidementia drugs	Baseline		
								HAM-D_{17}	MMSE	GAF
1	78	F	1	4	0	None		22	25	21
2	84	M	2	5	0	None	Nicergoline	16	15	35
3	79	F	1	4	1	Sulpiride, mianserin		21	23	25
4	79	F	2	5	0	None	Donepezil	24	22	35
5	71	F	2	6	0	None	Donepezil	19	9	25
6	81	F	1	4	0	None	Donepezil	16	17	45
7	77	F	1	4	0	None	Amantadine, nicergoline	12	22	65
8	79	F	2	4	0	None	Donepezil	17	22	31
9	84	M	0.5	4	0	None		16	21	35
10	59	F	1	4	0	None		16	18	25
11	56	F	2	4	0	None	Donepezil	22	19	25
12	58	M	1	4	0	None	Donepezil	17	22	35
13	69	M	1	4	0	None	Donepezil	13	19	51
14	86	F	2	5	0	None	Donepezil	21	16	25