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Do baseline WAIS-III subtests predict treatment outcomes for depressed inpatients receiving fluoxetine?

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ABSTRACT

This study aimed to determine whether baseline WAIS-III subtests could be associated with treatment outcomes for patients with major depressive disorder (MDD) receiving a 6-week fluoxetine treatment. A total of 131 acutely ill MDD inpatients were enrolled to receive 20 mg of fluoxetine daily for 6 weeks. Eight WAIS-III subtests were administered at baseline. Symptom severity and functional impairment were assessed at baseline, and again at weeks 1, 2, 3, 4, and 6 using the 17-item Hamilton Depression Rating Scale (HAMD-17) and the Modified Work and Social Adjustment Scale (MWSAS), respectively. The generalized estimating equations method was used to analyze the influence of potential predictors over time on the HAMD-17 and MWSAS, after adjusting for covariates. Of the 131 participants, 104 (79.4%) who completed 8 WAIS-III subtests at baseline and had at least one post-baseline assessment were included in the analysis. Patients with lower forward digit span scores were more likely to have poor treatment outcomes, both measured by HAMD-17, and by MWSAS. Forward digit span may be clinically useful in identifying MDD patients with greater treatment difficulty in symptoms and functioning. Other neurocognitive tests to predict treatment outcome require further exploration.

1. Introduction

Major depressive disorder (MDD) is a common mental disorder. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSMD-IV) (APA, 1994b) or the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (APA, 2013) identifies cognitive impairment (i.e., diminished ability to think or concentrate, or indecisiveness) as one criterion of a major depressive episode (MDE). These symptoms are comparable to impairment in neurocognitive functions such as memory, attention, executive functioning, or psychomotor speed (Culpepper et al., 2017). Some other depressive symptoms may mediate neurocognitive functions, including psychomotor retardation, fatigue, and mood disturbance (Lam et al., 2014). Cognitive impairment has been estimated to occur in about 2/3 of MDD patients (Butters et al., 2004; Rock et al., 2014).

An antidepressant medication is recommended as a treatment choice for patients with mild to severe MDD (Gelenberg et al., 2010). Several studies have explored baseline neurocognitive domains which potentially predict responses to antidepressants (Bortolato et al., 2014). If special domains could predict clinical response earlier, treating psychiatrists could then determine the best remedy for the patients earlier. For instance, psychomotor slowing may show greater response to bupropion (Herrera-Guzman et al., 2008) or may be less likely to respond to serotonin reuptake inhibitor (SSRI) monotherapy (Taylor et al., 2006b). Impaired performance on neurocognitive tests of executive function or psychomotor speed may predict poor response to antidepressants (Simpson et al., 1998; Kalayam and Alexopoulos, 1999; Dunkin et al., 2000; Alexopoulos et al., 2004; Majer et al., 2004; Alexopoulos et al., 2005; Gorlyn et al., 2008). Executive deficits in the elderly were worse response to antidepressant medication (Potter et al., 2004). The antidepressant responders were characterized by a lower ability to perform complex tasks but a better performance on simple tasks compared to nonresponders (Kampf-Sherf et al., 2004). However, evidence about the definitive baseline neurocognitive domain as a predictor of treatment outcome is still inconsistent. There are some explanations for these inconsistencies. First, lack of adjusting for confounding variables may influence the estimates. For example, cognitive functions are known to decline with age (Austin et al., 2001; Porter et al., 2007). Early age onset of MDD is associated with a greater likelihood of poor neurocognitive function (Castaneda et al., 2010).

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Patients with higher levels of education may experience less impairment in learning, memory, and attentional switching, and may therefore be correlated with higher neurocognitive function (Daniel et al., 2013; Russo et al., 2015). Also, the number of MDEs has been found to be related to cognitive decline (Kessing, 1998). Severe baseline depression has been correlated to lower neurocognitive function (McDermott and Ebmeier, 2009; Preiss et al., 2009; Snyder, 2013), and may also predict treatment outcome (Saghafi et al., 2007; Howland et al., 2008). Second, there is still no accepted "gold standard" neurocognitive test to measure neurocognitive function in MDD (McIntyre et al., 2013; Russo et al., 2015). The various neurocognitive tests employed may account for discrepancies among studies (Salagre et al., 2017). Third, studies without providing the powers for small sample sizes (14–55 subjects) (Kalayam and Alexopoulos, 1999; Dunkin et al., 2000; Kampf-Sherf et al., 2004; Taylor et al., 2006b; Gorlyn et al., 2008) or enrolling only elderly patients (Simpson et al., 1998; Alexopoulos et al., 2004; Potter et al., 2004; Alexopoulos et al., 2005) could restrict the interpretation of the results. Additionally, most studies used different categorical variables (i.e., response vs. non-response or remission vs. non-remission) as outcome measures. For example, improvement of at least 50% (Majer et al., 2004; Alexopoulos et al., 2005; Gorlyn et al., 2008; Herrera-Guzman et al., 2008) or 67% (Kampf-Sherf et al., 2004) in depressive symptoms after treatment were used to define response. The patients who no longer met the criteria for MDD and had a clinical global impression scale score of "much improved" or "very much improved" (Taylor et al., 2006b) or had a final 17-item Hamilton Depression Rating Scale (HAMD-17) (Hamilton, 1960) ≤ 10 (Dunkin et al., 2000), were also considered to be responders. The Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) <10 was considered a response in one study (Simpson et al., 1998). Remission was also defined in different ways: HAMD-17 ≤ 7 (Pluijms et al., 2002), HAMD-17 ≤ 8 (Medda et al., 2014), HAMD-17 ≤ 10 (Pande et al., 1988), MADRS <7 (Potter et al., 2004), 21-item HAMD ≤ 10 (Majer et al., 2004), 24-item HAMD <10 (Alexopoulos et al., 2004), or the Cornell Scale <7 (Kalayam and Alexopoulos, 1999). Based on statistical theory, any downscaling procedures (e.g., a continuous variable to a categorical variable) results in a loss of statistical power (Ragland, 1992; Streiner, 2002; Taylor et al., 2006a). Therefore, a statistical approach using continuous variables (e.g., HAMD scores) is preferable.

The American Psychiatric Association (APA) guideline for the treatment of patients with MDD (Gelenberg et al., 2010) emphasizes the importance of adding functional measures to adequately capture the full impact of depression and its treatment. It has been determined that depressive symptoms and functional impairment are distinct domains (Finkelstein et al., 1996; Judd et al., 2000; Papakostas et al., 2004; Lin et al., 2015a). Daily functioning is less emphasized in standard measures of depression severity, such as in HAMD-17. In clinical trials evaluating treatment for MDD, more attention is paid to symptom severity than to daily function (Lam et al., 2011). Several studies have found that neurocognitive function is a critical determination of daily functioning in MDD (Jaeger et al., 2006; Buist-Bouwman et al., 2008; McIntyre et al., 2013; Culpepper et al., 2017). McIntyre et al. (McIntyre et al., 2013) have indicated that cognitive impairment is associated with consistent and clinically significant impact on the symptomatic and functional outcomes. As with overall depressive symptoms, it is therefore important to assess the baseline cognitive function, as well as to regularly monitor daily functioning. Unlike using baseline neurocognitive function to predict the symptomatic outcomes mentioned above, whether the special baseline neurocognitive domain could predict functional outcome has never been explored.

The third edition of the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997) is the most frequently used neurocognitive test in clinical settings (Rabin et al., 2005). The aim of the present study was to identify whether baseline WAIS-III subtests could predict treatment outcomes for MDD patients treated with a 6-week course of fluoxetine. We hypothesized that the baseline neurocognitive test may contribute to the ineffectiveness of an antidepressant therapy, and impede functional improvement.

2. Methods

2.1. Subjects

The study was a post-hoc analysis of our previous clinical trial conducted from May 2007 to February 2010 and documented elsewhere (Lin et al., 2011; 2013). The trial was approved by Kai-Syuan Psychiatric Hospital's institutional review board and conducted in accordance with both Good Clinical Practice procedures and the most recent revision of the Declaration of Helsinki. Written informed consent was obtained from all participants after a full explanation of study aims and procedures. This study was registered on http://www.clinical.trials.gov (Identifier number: NCT01075529).

Briefly, all MDD patients ($N = 283$) newly hospitalized for acute treatment were screened and evaluated by board-certified psychiatrists using the Structured Clinical Interview for DSM-IV (APA, 1994a) to ensure diagnostic accuracy. Han Chinese patients in Taiwan were enrolled in this study if they: (1) were physically healthy with normal laboratory tests (including electrocardiography and chest X-ray), (2) were aged 18–70 years, and (3) satisfied DSM-IV criteria for MDD. The exclusion criteria were: (1) a baseline score of a 17-item Hamilton Depression Rating Scale (HAMD-17) (Hamilton, 1960) <18, (2) a Clinical Global Impression of Severity (Guy, 1976) <4, (3) psychotic depression, bipolar I or II disorder, schizophrenia or any other psychotic disorder, (4) a DSM-IV diagnosis of substance abuse or dependence (including alcohol) within the past 6 months, (5) mental disorders due to organic factors, (6) full scale IQ <50, (7) initiating or ending formal psychotherapy within six weeks prior to enrollment, (8) receiving formal psychotherapy during the trial period, (9) treatment-resistant depression (defined as a lack of response to 2 or more adequate courses of antidepressant treatment),(10) a history of poor response to fluoxetine (20 mg/day for ≥ 4 weeks) or intolerance to fluoxetine, (11) a history of electroconvulsive therapy, and (12) pregnancy or lactation.

2.2. Procedures and assessments

After a washout period of at least 72 h, patients received open-label fluoxetine treatment at a fixed dose of 20 mg daily for 6 weeks. No other psychotropic agents were administered during the treatment period, except for anxiolytic or sedative-hypnotic medications as needed for insomnia or severe anxiety. Treatment compliance was monitored and ensured by psychiatric nurses. Demographic and clinical characteristics of the participants were gathered at baseline. Age at onset was regarded as the age at which the first MDE occurred.

At baseline, patients were administered the Chinese version of WAIS-III (Wechsler et al., 2002) by a licensed clinical psychologist (the third author). The 8 WAIS-III subtests (i.e., similarities, information, forward digit span, backward digit span, picture completion, arithmetic, block design, and digit symbol) were obtained. The WAIS-III can be given to subjects aged 16–89 years. At the time of testing, the clinical psychologist was unaware of the patients' symptomatic and functional severity. The raw score of each WAIS-III subtest data was utilized for analysis.

Symptom severity was assessed at baseline, and again at weeks 1, 2, 3, 4 and 6 by board-certified psychiatrists, who were blind to the patients' neuropsychological tests, using the HAMD-17. HAMD-17 scores ranged from 0 to 52, with higher scores indicating greater severity of depressive symptomatology. The intra-class correlation coefficient (ICC) of reliability was 0.95 between the raters.

The Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002) is a self-rating scale, consisting of 5 items. It measures an individual's

perception of work and social functioning, with higher scores representing greater impairment of functioning. Each item is scored from 0 (not affected at all) to 8 (severely affected). Item 1 is used to assess work ability. However, since it may be difficult to demonstrate a high level of work functioning while in the hospital when the patients' jobs are outside of the hospital, or for those patients who have retired, Item 1 has been omitted. The Work and Social Adjustment Scale, without Item 1, has been designated the Modified Work and Social Adjustment Scale (MWSAS) for the present study, and used to measure functioning at weeks 0, 1, 2, 3, 4, and 6. MWSAS has been used in our previous studies to measure inpatients' functioning (Lin et al., 2015a; 2015b).

2.3. Statistical analysis

Analysis was on a modified intent-to-treat basis. Patients were included in analysis only if they completed 8 WAIS-III subtests at week 0 and had at least one post-baseline assessment of HAMD-17 and MWSAS. First, we conducted descriptive statistics to summarize the data (i.e., percentages, means, SDs, and range).

Second, because all subjects were MDD patients newly hospitalized for acute treatment, baseline WSA can reflect the work functioning before admission. The internal consistency (i.e., reliability) of MWSAS at baseline was determined using Cronbach's alpha (Cronbach and Warrington, 1951). A value of Cronbach's alpha ≥ 0.70 is considered to be acceptable. Pearson's correlation coefficient (r) was employed to quantify the association between baseline WSAS and baseline MWSAS. A strong association (i.e., high validity) has been defined as an $r > 0.70$ (McHorney et al., 1993).

Third, paired *t* test was used to compare score changes in HAMD-17 and MWSAS at each assessment. Effect size was defined as the difference in the mean score between baseline and each assessment (i.e., at weeks 1, 2, 3, 4, and 6) divided by the pooled standard deviation (Morris and DeShon, 2002). A d-value of 0.20 indicates a small effect size, 0.50 a medium effect size, and 0.80 a large effect size (Cohen, 1988). Large effect sizes indicate clinically relevant improvements at the end point.

Fourth, the generalized estimating equations (GEEs) method with first-order autoregressive working correlation structure (Liang and Zeger, 1986) was used to analyze the influence of potential variables over time on the HAMD-17 and MWSAS respectively, after adjusting for covariates. Covariates included sex (Hines, 2010), age (Austin et al., 2001), educational level (Daniel et al., 2013; Russo et al., 2015), age at onset (Castaneda et al., 2010), number of previous MDEs (Kessing, 1998; Paelecke-Habermann et al., 2005; Talarowska et al., 2015), 8 WAIS-III subtests, and baseline severity (baseline HAMD-17 or baseline MWSAS) (Preiss et al., 2009; Snyder, 2013).

Fifth, in clinical practice, response and remission are traditionally regarded as treatment outcomes for patients with MDD. The goal of antidepressant therapy is to reach symptomatic remission (Gelenberg et al., 2010). Response was defined as at least a 50% reduction of the HAMD-17 score, and remission as HAMD-17 ≤ 7 (Pluijms et al., 2002) after acute treatment with fluoxetine.

All tests were two-tailed, and statistical significance was set at $p < 0.05$. All data were processed by the SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

A total of 131 acutely ill inpatients with major depressive disorder agreed to participate in this 6-week fluoxetine trial. Of the 131 participants, 104 (79.4%), who completed 8 WAIS-III subtests at week 0 and had at least one post-baseline assessment for HAMD-17 and MWSAS, were included in the analysis. Table 1 lists the baseline characteristics, raw subtest scores of WAIS- III, verbal IQ, performance IQ, and full scale IQ. The Cronbach's alpha of baseline MWSAS was 0.85. It indicated that baseline MWSAS had acceptable reliability. Baseline WSAS was highly correlated with baseline MWSAS ($r = 0.99$). Baseline MWSAS had validity comparable with baseline WSAS. Mean scores (SD), *p* values of paired *t* test, and effect sizes of HAMD-17 and MWSAS at each assessment were shown in Table 2. The mean HAMD-17 (SD) of score of 30.7 (6.6) at baseline reflected a fairly severely depressed population.

Table 1
Baseline characteristics and raw subtest scores of WAIS-III [a] ($n = 104$).

Variables	Distribution	Range
Sex-male, *n* (%)	26 (25.0)	
Age, mean (SD), year	44.2 (10.6)	20–69
Young adults (20–39 y/o), *n* (%)	35 (33.35)	
Middle adults (40–64 y/o), *n* (%)	67 (63.8)	
Old adults (≥ 65 y/o), *n* (%)	3 (2.9)	
Educational level,, mean (SD), year	11.3 (3.4)	0–18
Young adults	12.6 (2.2)	6–18
Middle adults	10.9 (3.6)	0–18
Old adults	6.0 (0.0)	6–6
Age at onset of illness, mean (SD), year	37.9 (12.0)	2– 63
Number of previous MDEs [b],, mean (SD)	2.4 (1.9)	0–6
WAIS-III subtest		
Similarities	13.6 (6.0)	0–28
Information	7.1 (3.4)	3–22
Arithmetic	10.2 (3.7)	3–19
Forward digit span	11.3 (3.2)	2 –16
Backward digit span	6.4 (2.8)	1–20
Picture completion	12.4 (5.7)	0–22
Block design	27.3 (10.6)	3–56
Digit symbol	54.8 (23.1)	3–110
Verbal IQ [c]	88.8 (13.7)	53–126
Performance IQ	83.7 (14.7)	39–116
Full Scale IQ	86.4 (12.9)	53–123

[a] WAIS-III = the third edition of the Wechsler Adult Intelligence Scale.
[b] MDE = major depressive episode.
[c] IQ = intelligence quotient.

3.2. Symptoms

For symptom severity measured by HAMD-17, the GEE method was used to examine the effects of potential predictors over time on HAMD-17. After adjusting for covariates, only WAIS-III forward digit span revealed a significant predictor of fluoxetine response. Each point increase on the forward digit span in treatment duration significantly decreased post-treatment HAMD-17 by, on average, 0.65 point (Table 3).

3.3. Functioning

Similarly, for functioning rated by MWSAS, the GEE method was used to examine the effects of potential predictors over time on MWSAS, adjusting for covariates. However, forward digit span was still the significant predictor. MWSAS significantly decreased by 0.53 point with each one point increase on the digit span forward. Another significant predictor was age (Table 4).

3.4. Response and remission

Fifty-six (53.8%) and 27 (26.0%) patients reached final response and remission after fluoxetine treatment, respectively. Baseline forward digit span was still a significant predictor associated with response (estimate = 0.25, odds ratio = 1.28, 95% CI,1.12–1.47, $p < 0.001$) and remission (estimate = 0.17, odds ratio = 1.19, 95% CI,1.003–1.41, $p = 0.046$) after adjusting for covariates using the GEE method.

Table 2
Mean scores, p values of paired t test, and effect sizes of HAMD-17[a] and MWSAS[b] at each assessment.

	Week 0 (n = 104)	Week 1 (n = 104)	Week 2 (n = 100)	Week 3 (n = 99)	Week 4 (n = 98)	Week 6 (n = 94)
HAMD-17, mean ± SD	30.7 ± 6.6	21.1 ± 8.0	17.4 ± 8.0	15.9 ± 8.6	14.9 ± 8.5	13.8 ± 8.3
P[c]		<0.001	<0.001	<0.001	<0.001	<0.001
Effect size		1.35	1.76	1.86	1.90	2.12
MWSAS, mean ± SD	23.8 ± 7.8	20.4 ± 8.4	18.1 ± 8.9	16.8 ± 9.6	16.3 ± 9.7	17.6 ± 10.5
P[c]		<0.001	<0.001	<0.001	<0.001	<0.001
Effect size		0.50	0.68	0.76	0.76	0.60

[a] HAMD-17 = 17-item Hamilton Depression Rating Scale.
[b] MWSAS = Modified Work and Social Adjustment Scale = Work and Social Adjustment Scale (WSAS) without Item 1.
[c] Paired t test = mean scores at weeks 1, 2, 3, 4, and 6 compared to mean scores at week 0.

4. Discussion

Our findings suggest that higher baseline scores of forward digit span predict better treatment outcomes for MDD patients taking fluoxetine, regardless of whether HAMD-17 or MWSAS scores are used as outcome measures. We also found that older age predicted greater functional improvement. Social functioning, rather than work functioning, was measured in the present study. The potential role of age on functional improvement should be clarified in future studies.

Multicollinearity is a phenomenon when two or more predictors are strongly correlated. If this happens, the standard error of the coefficients will increase greatly (McClendon, 2002). In simple model with one WAIS-III subtest (Daoud, 2017) rather than 8 WAIS-III subset together (i.e., multiple model), the GEE method was used to examine the effect of each of the WAIS-III subtest over time on HAMD-17 after adjusting for sex, age, educational level, age at onset, number of previous MDEs, and baseline HAMD-17. The standard errors of coefficients have not changed dramatically (data not shown in the table). For example, there is a significant correlation between similarities subtest and picture completion subtest (r = 0.673, p < 0.001), for similarities subtest from 0.09 to 0.11 for simple and multiple model (Table 3), and for picture completion subtest from 0.11 to 0.13. Similarly if using MWSAS as outcome measure, the standard errors of coefficients have also not changed dramatically (data not shown in the table), for similarities subtest from 0.11 to 0.14 for simple and multiple model (Table 4), and for picture completion subtest from 0.12 to 0.15. Therefore, the problem of multicollinearity in the present stud did not give cause for concern.

Our result with regard to forward digit span was comparable to the study by Potter et al. (2004). They found that depressed elder patient with low forward digital span score at baseline was associated with a significant lower remission (i.e. MADRS ≥7) rate after 3 months of antidepressant treatment. Another study by Taylor et al. (2006b) showed that patients with fluoxetine responders had larger observed score of total digit span (11.44 ± 3.24 vs. 10.42 ± 2.91) than non-responders. The other study (Majer et al., 2004) revealed that after antidepressant treatment, responders (7.5 ± 2.0 vs. 7.2 ± 2.2) or remitters (7.6 ± 2.2 vs. 7.0 ± 2.0) had higher observed forward digit span score than non-responders or non-remitters, respectively. These findings indicated that forward digit span score may contribute treatment outcome to a certain extent.

In Forward Digit Span, the participant is required to repeat a string of numbers in the same order immediately as read aloud by the examiner. This immediate recall of digits taps upon short-term verbal memory which involves concentration and sustained attention (Groth-Marnat, 2000; Miyake and Friedman, 2012; Vicent-Gil et al., 2018). A deficit in Forward Digit Span may be associated with maintaining a mental set in the face of distracting affective input (Potter et al., 2004). This finding implies that neurocognitive mechanisms subserving verbal short-term memory may, to a certain extent, be related to the pharmaceutical mechanism of fluoxetine or other SSRIs in general. SSRIs also have been reported to affect cortical and subcortical regions involved in verbal short-term memory (Smith et al., 2011). The interaction among serotonin, verbal short-term memory, and clinical response

Table 3
Effects of potential predictors over time on HAMD-17 score, after mutually adjusting for covariates using generalized estimating equations.

Variable	Estimate	SE[a]	95% C.I.[b]	p
HAMD-17				
Week 0	0	.	.	.
Week 1	−9.69	0.71	−11.08 ~ −8.30	<0.001
Week 2	−13.30	0.751	−14.77 ~ −11.83	<0.001
Week 3	−14.79	0.791	−16.35 ~ −13.235	<0.001
Week 4	−15.86	0.84	−17.50 ~ −14.21	<0.001
Week 6	−16.98	0.81	−18.58 ~ −15.40	<0.001
Sex (male vs. female)	0.49	0.73	−0.94 ~ 1.93	0.500
Age (1-year increment)	−0.10	0.07	−0.23 ~ 0.03	0.115
Educational level (1-year increment)	−0.27	0.15	−0.56 ~ 0.03	0.075
Age at onset (1-year increment)	0.06	0.05	−0.05 ~ 0.16	0.299
Number of previous MDEs	0.07	0.21	−0.35 ~ 0.49	0.759
Baseline similarities (1-point increment)	0.20	0.11	−0.02 ~ 0.40	0.069
Baseline information (1-point increment)	0.17	0.09	−0.01 ~ 0.351	0.058
Baseline arithmetic (1-point increment)	−0.16	0.15	−0.46 ~ 0.15	0.312
Baseline forward digit span (1-point increment)	−0.65	0.16	−0.96 ~ −0.035	<0.001
Baseline backward digit span (1-point increment)	0.10	0.15	−0.19 ~ 0.39	0.484
Baseline picture completion (1-point increment)	0.22	0.13	−0.03 ~ 0.47	0.087
Baseline block design (1-point increment)	−0.06	0.05	−0.17 ~ 0.05	0.256
Baseline digit symbol (1-point increment)	0.02	0.03	−0.05 ~ 0.08	0.585
Baseline HAMD (1-point increments)	0.75	0.06	0.63 ~ 0.88	<0.001

[a] SE = standard error.
[b] C.I. = confidence interval.

Table 4
Effects of potential predictors over time on MWSAS score, after mutually adjusting for covariates using generalized estimating equations.

Variable	Estimate	SE	95% C.I.	*p*
MWSAS				
Week 0	0	.	.	.
Week 1	−3.44	0.67	−4.75 ~ −2.14	<0.001
Week 2	−5.67	0.81	−7.26 ~ −4.08	<0.001
Week 3	−6.90	0.88	−8.64 ~ −5.17	<0.001
Week 4	−7.43	0.96	−9.30~ −5.55	<0.001
Week 6	−6.20	1.03	−8.23 ~ −4.18	<0.001
Sex (male vs. female)	−0.61	1.09	−2.74 ~ 1.52	0.576
Age (1-year increment)	−0.17	0.06	−0.29 ~ −0.05	0.004
Educational level (1-year increment)	−0.27	0.21	−0.69 ~ 0.15	0.201
Age at onset (1-year increment)	0.04	0.05	−0.06 ~ 0.13	0.464
Number of previous MDEs	0.33	0.25	−0.17 ~ 0.82	0.198
Baseline similarities (1-point increment)	0.25	0.14	−0.03 ~ 0.53	0.078
Baseline information (1-point increment)	0.10	0.16	−0.21 ~ 0.42	0.517
Baseline arithmetic (1-point increment)	−0.11	0.19	−0.48 ~ 0.27	0.570
Baseline forward digit span (1-point increment)	−0.53	0.20	−0.92 ~ −0.15	0.007
Baseline backward digit span (1-point increment)	0.25	0.21	−0.15 ~ 0.66	0.224
Baseline picture completion (1-point increment)	−0.002	0.15	−0.29 ~ 0.29	0.988
Baseline block design (1-point increment)	0.03	0.05	−0.07 ~ 0.14	0.547
Baseline digit symbol (1-point increment)	−0.03	0.04	−0.12 ~ 0.06	0.553
Baseline MWSAS (1-point increments)	0.68	0.06	0.57 ~ 0.79	<0.001

should be examined in future studies. The forward digit span test is non-invasive, is inexpensive, and is easily and quickly performed, so it is particularly user friendly in a clinical setting (Jasinski et al., 2011).

Patients in the current study received the same fixed dose, 20 mg daily, of fluoxetine. Earlier fixed-dose studies (Schweizer et al., 1990; Stokes, 1993) have indicated that 20 mg daily of fluoxetine is the optimal dose for most depressed patients. A meta-analysis study (Beasley et al., 2000) also found that fluoxetine treatment at 20 mg daily is a critical factor for adequate therapy and has good treatment tolerance. A flat dose-response curve is considered a classic phenomenon for SSRIs, regardless of whether patients have mild or moderate-to-severe depression (Berney, 2005). However, the rates and quality of responses to fluoxetine are highly individualized.

Several strengths of this study should be addressed. First, all covariates that may contribute to the estimates have been adjusted. Therefore, any statistical significances occurred by chance were negligible. Second, outcome measures included symptoms and functioning. Third, this was a repeated measure study. Therefore longitudinal follow-up data were obtained from the same subjects. The GEE method is powerful because it requires no assumptions about data distribution, capitalizes on maximal data, and adjusts for the within-subject dependence effect (Madhoo and Levine, 2015).

However, our findings should be interpreted with caution due to certain limitations. First, this was an uncontrolled, open-label study. It was difficult to establish the degree to which clinical improvements were due to fluoxetine treatment, placebo effect, or other psychiatric interventions. For example, hospitalization itself can be a significant non-pharmacological therapeutic factor affecting clinical improvement in patients with MDD. Therefore, this study did not establish a causal link between fluoxetine and any changes observed, since no control group was present. Without a placebo-controlled group, the impact of placebo effects on the current study could not be estimated. However, it is unlikely the clinical response was solely attributable to placebo effects for the following reasons: one, the response (i.e., a reduction of 50% or more of the HAMD-17) rate (=53.8%) was too high to be accounted for by typical placebo effects, i.e., around 30%, as estimated from past clinical placebo-controlled antidepressant trials (Walsh et al., 2002); two, it has been demonstrated that patients with more severe depression are less susceptible to the placebo effect (Khan et al., 2002). Second, because the sample size was relatively low, the present results should be replicated in independent studies with larger sample sizes. Third, there was no matching healthy control group. Fourth, the study period of 6 weeks is relatively short when considering the total duration of depression. However, it is relatively long and sufficient for inpatient trials to detect initial antidepressant responses. Long-term follow-up after hospitalization would allow further elucidation as to whether the differences persist beyond the study period. Fifth, only 8 WAIS-III subtests were used to predict treatment outcomes in the present study, we did not know whether other WAIS-III subtests such as symbol search and matrix reasoning would be the significant predictor(s). Furthermore, since the WAIS-III is a test of general intellectual ability, it may not be sufficiently sensitive to measure the specific neuropsychological domains of MDD patients (Gorlyn et al., 2006). Consequently, neuropsychological tests that measure more narrowly defined aspects of cognitive functioning may be necessary. Sixth, use of an all-Taiwanese sample may limit generalizability to other countries. Seventh, only patients who were physically healthy were included for analysis, and smoking is completely prohibited in the hospital according to Taiwan's Tobacco Hazards Prevention Act. Hypertension, diabetes, and smoking that are potential risk factors of cognitive decline (Yaffe et al., 2004; Craft, 2009; Durazzo et al., 2010) were not regarded as covariates for adjusting in the preset study. Finally, the predictive value of the finding does not necessarily generalize to antidepressants other than fluoxetine.

In conclusion, forward digit span may be useful in identifying MDD patients whose neurocognitive functions in this test predisposed them to greater treatment difficulty with regards to symptom and functioning. Routine neurocognitive test before antidepressant use is suggested. Other neurocognitive tests to predict outcomes for MDD patients treated with antidepressants that will ultimately make possible more personalized treatments and prognoses require further exploration in future studies.

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