

## Attention, Concentration and Planning Ability Improvement in Response to Depression Treatment during Acute Psychiatric Hospitalization

Luba Leontieva<sup>1\*</sup>, Sergey Golovko<sup>2</sup>, Aadhar Adhlakha<sup>3</sup>, Lyuba Polinkovsky<sup>4</sup>, Charles Harris<sup>6</sup>, Donald A Cibula<sup>5</sup> Thomas Schwartz<sup>1</sup> and James L Megna<sup>1</sup>

<sup>1</sup>Department of Psychiatry, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY, USA

<sup>2</sup>Central New York Psychiatric Center, Marcy, NY, USA

<sup>3</sup>Detroit Medical Center, Detroit, MI, USA

<sup>4</sup>Stamford Hospital, Columbia University Family Medicine, CT, USA

<sup>5</sup>Department of Public Health and Preventive Medicine, SUNY Upstate Medical University, Syracuse, NY, USA

<sup>6</sup>St. Lawrence Psychiatric Center, Ogdensburg, NY, USA

\*Corresponding author: Leontieva L, Department of Psychiatry, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY, 13210, USA, Tel: 315-464-3278; E-mail: [LeontieL@upstate.edu](mailto:LeontieL@upstate.edu)

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### Abstract

**Background:** Cognitive symptoms are some of the most distressing for patients who are depressed. The goal was to investigate whether depressed patients' cognition changed depending on treatment with SSRIs (No-NOR) vs. Norepinephrine-enhancing medications (NOR) during an inpatient stay.

**Methods:** This was an observational, naturalistic, pilot study that used a repeated measures design. 119 depressed inpatients, average age 39 years, 61% females, 77% Caucasian, 74% with mood disorders, 50% Cluster B traits/disorders and 32% psychoactive substance abuse disorders participated. The Trail Making Test (TMT), Hamilton Depression Rating Scale (HDRS), and Outcome Questionnaire-45(OQ-45) were used.

**Results:** Revealed significant differences between admission and discharge in HDRS (MA=24, MD=9, t (98)=25.30, p<0.001), and OQ-45 (MA=105, MD=72, t (97)=12.91, p<0.001) scores. Mean time to complete the TMT-A at discharge for all NOR patients was 32.92 ± 22.47 seconds, and was significantly shorter than the comparable mean for the No-NOR group (39.10 ± 18.88 seconds, t=-2.33, p=0.022).

**Conclusion:** Patients taking SNRIs, alone or in combination with benzodiazepines, Seroquel or TCAs (NOR), had significantly shorter completion times for the TMT-A test at discharge than did patients taking SSRIs, with or without benzodiazepines (No-NOR). This cognitive improvement developed independently of significant reductions in depressive symptomatology and interpersonal/social functioning impairment.

**Keywords:** Depression; Cognition; SNRIs; Inpatient

### Introduction

"Diminished ability to think or concentrate" is one of the DSM-5 criteria for major depression [1]. Attention, concentration, and memory are essential abilities for a person to be able to plan, function, and be productive in life. Cognitive symptoms are one of the most distressing for patients who are depressed [2,3]. One study of 77 depressed inpatients found that poorer cognitive functioning is associated with poorer instrumental activities of daily living [4]. One recent study showed that impairment in such pre-frontal tasks as sustained attention and psychomotor dexterity could be seen in young, untreated individuals with depression [5]. An improvement in these cognitive abilities with treatment of depression is important for a patient to get better in emotional information processing and, consequently, to be more emotionally available in therapy and in relationships [6]. Motor speed improvement in depression treatment may also be an indication that treatment is working.

Depression is associated with disturbance of serotonin (5-HT), norepinephrine (NE), and dopamine (DA) neurotransmitters in the central nervous system [7,8]. This is known as the monoamine hypothesis of depression. Antidepressants that target depressive symptoms are serotonergic, norepinephrergic and dopaminergic in their mechanisms of action. Reduced NE levels are related to problems with attention, concentration, cognitive sharpness, slow processing speed (executive functioning), and low energy; reduced DA levels are correlated with anhedonia, motivation, and reward; low 5-HT levels lead to anxiety and obsessive-compulsive tendencies [9]. The executive functioning region in the brain is the prefrontal lobe of the cortex and its afferent and efferent structures involving the neurotransmitters NE and DA, and to a lesser degree acetylcholine and 5-HT [10].

Executive function is very important in social relationships and adaptation. Social dysfunction in depression may be one of the most important factors affecting the quality of life of patients. NE improvement in depression has been studied and is associated with significant clinical and functional improvements [10]. Considerable clinical data suggest the importance of NE in the improvement of clinical dysfunction in depression [11].

One group of researchers Kessler, et al. [12] found that patients with depression in the context of Bipolar I Disorder have global neurocognitive difficulties, in particular diminished processing speed. Another group Douglas, et al. [13] found that pervasive neuropsychological impairment was evident at baseline in patients with depression compared with that of healthy controls. Furthermore, during 6 weeks of treatment with antidepressants simple reaction time, verbal working memory and the recognition of angry facial expressions showed differential changes. One research group Herrera-Guzmán, et al. [14] showed that treatment with escitalopram and duloxetine (both 5-HT/NE reuptake inhibitors) improved working memory, attention, and other executive functioning in depressed individuals. Another study Gualtieri, et al. [15] reported that depressed patients on bupropion performed as well as normal controls compared to impaired performance of depressed patients on Selective Serotonin Reuptake Inhibitors (SSRIs) and venlafaxine (SNRI). Another study Roy, et al. [16] found that symptomatic improvement in depression treatment with citalopram positively correlates with picture recognition memory accuracy, for which ventromedial prefrontal and anterior cingulate cortices are responsible. Thus, depression treatment with different medications influences changes in cognitive functioning of depressed individuals.

Antidepressants are widely used during inpatient stays. The rationale for selecting the particular type of antidepressant depends on the most salient symptoms (i.e., anxiety, amotivation), co-occurring conditions (i.e., substance use), prior success with particular medication, and side effects tolerability. The biological rationale for a NE enhancing antidepressant stems from the fact that Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) agents combine the effect of serotonin transporter inhibition of the Selective Serotonin Reuptake Inhibitors (SSRIs) with various degree of inhibition of the norepinephrine transporter, plus boosting dopamine in prefrontal cortex. All these benefits can help treat depression faster and improve executive functioning.

Little is known about improvement in cognition in depressed patients during the shorter duration of an inpatient stay on the psychiatric floor of a general hospital. The present study explores whether there are changes in cognitive performance in patients who are depressed during treatment on an inpatient unit.

The primary aim of this study is to identify the degree of impairment and changes in attention, concentration, motor speed, planning ability, and associated memory, as well as in depression symptom level and quality of life in patients with depression. Patients were compared to their own performance at baseline (prior to initiating treatment) and prior to discharge from the inpatient unit. The study investigates how certain diagnoses and medications correlate with the degree of depressive and cognitive changes. We hypothesize that those patients who receive dopaminergic and norepinephrinergic medications will have greater improvement in their attention, concentration, speed of processing, organization, and associative memory compared to patients on SSRIs.

## Methods

Study participants were selected from an acute inpatient psychiatric unit (24 beds) of an academic hospital in central New York. The hospital is located in a city with a population of approximately 147,000 people. The unit takes admissions from the Emergency Room, medical/surgical floors, and the local psychiatric emergency room (at

another hospital in the city). The unit admits an average of 75 patients per month. Patients who were eligible for admission to the unit were those who had acute psychiatric symptoms requiring inpatient admission (i.e., suicidality, self-harm, psychosis, severe depression, mania, etc.). Study participants included 119 patients who were admitted to the unit from February 2012 to July 2013 and reported depression on admission. Exclusion criteria were acute intoxication/withdrawal from substances, delirium, documented mental retardation, and dementia.

This was an observational, naturalistic, pilot study that used a repeated measures design. There was no random assignment to different groups (i.e., diagnostic groups, medication type groups, etc.). Instead, we enrolled patients per the above criteria and followed them throughout their course of treatment as provided by their primary care teams.

## Measures

- Hamilton Depression Rating Scale (HAM-D) (17 questions version)-to assess depression level [17]. It is a well-researched scale with established psychometric properties and is most commonly used for depression evaluation [18,19]. The HAM-D is a clinician-rated scale and the scores range from 0 to 52. Scores from 0-7 indicate no depression; 8-13-mild depression; 14-18-moderate depression; 19-22-severe depression; >23-very severe depression.
- Outcome Questionnaire (OQ-45) to assess level of symptom distress, interpersonal functioning, and social role [20].
- Trail Making Test (TMT, parts A and B) to assess attention, concentration, speed of processing, and visual-spatial dexterity [21]. Two alternative versions of the PT (see below) and TMT will be used pre- and post-assessment to eliminate a practice effect [22].
- The Pictogram Test (PT)-to assess associated memory and speed of processing [23]. More information on this test can be found elsewhere [23]. Briefly, in this test 16 words were presented one by one to the patient. The task was to draw a picture that will help to recall the words after a 1 hour delay. After 1 hour the patient was given the drawings back and asked to recall the words. The recall, speed of processing, and association's type selected for memorization was analysed. For the purpose of this study we report only memorization and the speed of processing time. Further results of this test will be reported in a separate paper.

## Procedure

The study was approved by the Institutional Review Board (IRB) and is in accordance with requirements as set forth in the Declaration of Helsinki. After agreeing to participate and signing the IRB Consent Form, participants completed the study measures at pre- (within 1-2 days of being admitted to inpatient unit) and post- (prior to discharge from the unit) time points. The assessments were conducted by two psychiatry residents and two psychiatrists well trained on all the measures of administration and scoring. The assessors were not the treating physicians for the study patients. They had no involvement in the study patients' treatment. Patients were provided verbal feedback on their performance if such was requested by them. The patients' medications were adjusted according to the treatment needs and independently from study participation.

**Statistical analysis**

The dependent variables were scores on the tests. The independent variables were types of psychiatric medications and psychiatric diagnoses. Mixed linear model regression using baseline Trail Making Test (TMT) scores as a covariate was used to estimate the differential effect of SSRIs and SNRIs on change in TMT-A and TMT-B scores between baseline and discharge. The following combinations of SSRIs, Selective Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and adjunctive medications at discharge (benzodiazepines, quetiapine, Tricyclic Antidepressants (TCAs), and buspirone and Norepinephrine Dopamine Reuptake Inhibitors (NDRIs) were tested as potential independent variables: 1) SSRIs vs. SNRIs alone; 2) SSRIs with or without (±) benzodiazepines vs. SNRIs ± benzodiazepines; 3) SSRIs ± benzodiazepines vs. SNRIs ± benzodiazepines ± each of the other listed adjuncts, in all possible combinations. The combination of drugs for the independent variable that produced the best maximum likelihood estimates for within and between subject variation in TMT A and TMT B scores [i.e., the 'best-fitting' model, judged by maximum likelihood ratios, Akaike's Information Criterion (AIC) and Schwarz's Bayesian Criterion (BIC)] was found to be SSRIs ± benzodiazepines (hereafter the 'No-Norepinephrine Group', No-NOR) vs. SNRIs ± benzodiazepines ± Seroquel ± TCAs (hereafter the 'Norepinephrine Group', NOR) for both TMT A and TMT B with mood disorder. For TMT B, and all diagnoses, the combination of SSRIs ± benzodiazepines vs. SNRIs ± benzodiazepines produced the best-fitting model. All final models included time, drug group and the time by drug group interaction terms. Inclusion of buspirone and NDRIs reduced model fit in all cases. Analysis was stratified by two primary diagnosis groups: (1) patients with mood disorder and (2) patients with any diagnosis. Statistical significance was demonstrated by a p value <0.05 (two-tailed). No correction for multiple testing was performed since the current investigation is a pilot study.

**Results**

One hundred and nineteen non-consecutive patients participated in the study. Twenty one did not complete the discharge measures because they were either rapidly discharged prior to final assessment or refused to complete the measures. This amounted to an 18% drop out rate.

Socio-demographic characteristics of study participants are presented in Table 1. Briefly, participants were mostly Caucasian,

around 40 years of age and had 12 years of education. Over half were on disability and unemployed; most were living independently or with family members.

	N	%
<b>Gender</b>		
Females	73	61
<b>Race</b>		
Caucasian	92	77
African American	18	15
Hispanic	6	5
Other	3	3
<b>Marital status</b>		
Single	54	45
Married/Partnership	34	29
Divorced/separated/widowed	31	26
<b>Disability income</b>		
Unemployed	81	68
<b>Living arrangements</b>		
Independent/with family	103	87
	Mean	SD
Years of education	13	2
Age	39	13

**Table 1:** Socio-demographic characteristics of the study participants.

Clinical characteristics of study participants are presented in Table 2. Briefly, most participants had Mood Disorders as a primary diagnosis; over one third had Borderline Personality Disorder; half had cluster B traits; almost one third had current substance use disorders. Less than one third were on SNRIs. Very few were on a TCA or bupropion. One third was on various atypical antipsychotics.

	N	%
<b>Axis 1 Primary Diagnosis</b>		
Mood Disorders	88	74
Psychotic Disorders	18	15
Anxiety Disorders	7	6
Substance Induced Disorders	5	4
<b>Axis 2 Diagnosis</b>		
Borderline Personality Disorder	42	35
Cluster B traits and/or disorders	59	50
<b>Substance use status</b>		

Current (last 6 months)	38	32
Past (prior to last 6 months or more)	15	13
Medications at baseline assessment		
Antidepressants		
SSRI	40	34
SNRI	24	20
NDRI	9	8
TCA	4	3
Trazodone	37	31
Mirtazapine	5	4
Buspirone	5	4
Antipsychotics		
Atypical	40	34
Typical	13	11
Mood Stabilizers	30	25
Benzodiazepines	45	38
	Mean	SD
Age of first psychiatric hospitalization	28	13
Length of stay during the current psychiatric admission	9	6
SSRI: Selective Serotonin Reuptake Inhibitors; SNRI: Selective Norepinephrine Reuptake Inhibitors; NDRI: Norepinephrine Dopamine Reuptake Inhibitors; TCA: Tricyclic Antidepressants		

**Table 2:** Clinical characteristics of study participants.

Table 3 displays the changes in measures between baseline and discharge. In summary, patients' depression scores improved dramatically, as well as their functioning scores. As a group, all patients improved their TMT scores as well as speed of completion of the PT. Memorization on the PT just reached significant difference. The other statistical data on the PT will be reported elsewhere.

Tests	Baseline		Discharge		n	95% CI for Difference	p
	M	SD	M	SD			
Hamilton Depression Scale Total score	23.9	6.8	8.6	4.9	98	-30.6	<0.001
Trail Making Test							
Trail A	49.5	30.2	37.2	16.7	98	-24.7	<0.001
Trail B	124.7	101.6	102.1	64.5	97	-45.1	0.006
OQ45							
Total score	104.7	22.1	71.7	28.4	98	-65.9	<0.001
Symptoms Distress Score	62.7	14.9	41.4	17.5	98	-42.7	<0.001
Interpersonal Relationship Score	23.3	7.1	16.9	8.1	98	-13	<0.001
Social Role Score	18.6	6.8	12.5	5.5	98	-54.4	<0.001

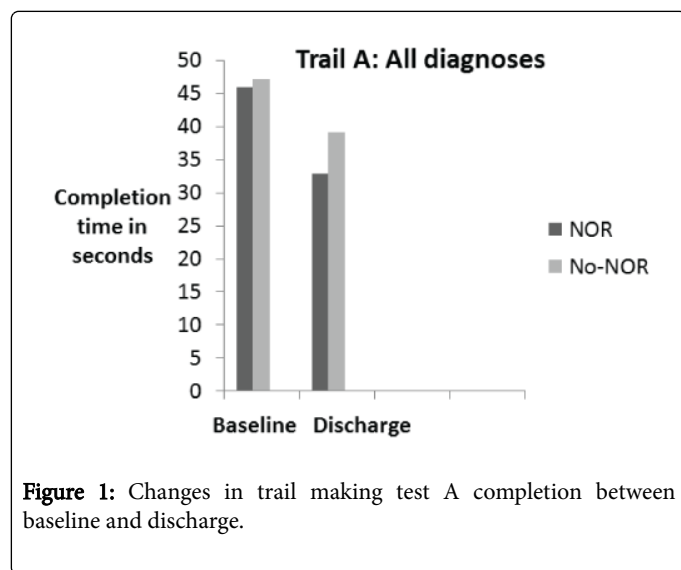
The Pictogram Test							
Memorization	8.7	3.9	8.1	3.5	98	-1.11	0.046
Completion Time in seconds	501.7	300.6	387.8	221.9	98	-227.8	<0.001

**Table 3:** Changes in test scores during the inpatient stay (paired t-test).

### Trail making test A

**All diagnosis:** Mean time to complete the TMT A at discharge for all NOR patients was  $32.92 \pm 22.47$  seconds, and was significantly shorter than the comparable mean for the No-NOR group ( $39.10 \pm 18.88$  seconds,  $t=-2.33$ ,  $p=0.022$ ). Mean time for the NOR group to complete the TMT A at baseline ( $45.96 \pm 19.78$  seconds) was not significantly different than the baseline mean for the No-NOR group ( $47.13 \pm 17.89$  seconds,  $t=0.48$ ,  $p=0.630$ ) (Figure 1).

**Mood disorder diagnosis:** Baseline-adjusted mean time to complete the TMT A at discharge was shorter for NOR patients ( $32.96 \pm 20.71$  seconds) than for No-NOR patients ( $38.24 \pm 18.61$  seconds,  $t=-1.87$ ,  $df=97$ ,  $p=0.065$ ). Mean completion time at baseline for the NOR group ( $44.53 \pm 18.29$  seconds) was not significantly different than the comparable mean for the No-NOR group ( $45.84 \pm 17.99$  seconds,  $t=0.51$ ,  $p=0.618$ ).



**Figure 1:** Changes in trail making test A completion between baseline and discharge.

### Trail making test B

**All diagnosis:** Mean time to complete the TMT B at discharge for patients taking SNRIs  $\pm$  benzodiazepines was  $94.67 \pm 176.92$  seconds, and was not significantly different than the comparable mean for patients taking SSRIs  $\pm$  benzodiazepines ( $110.89 \pm 155.69$  seconds,  $t=0.329$ ,  $p=0.696$ ). No difference in TMT B means was observed for the baseline tests; the mean for SNRIs  $\pm$  benzodiazepines was  $104.31 \pm 133.70$  seconds, compared with  $125.05 \pm 97.08$  seconds for the SSRIs  $\pm$  benzodiazepines group ( $t=0.98$ ,  $df=73$ ,  $p=0.552$ ).

**Mood disorder diagnosis:** At discharge, there was no difference in mean time to complete the TMT B test for the NOR group ( $107.29 \pm 78.88$  seconds) compared to the No-NOR group ( $100.05 \pm 70.99$  seconds,  $t=0.69$ ,  $p=0.495$ ). Likewise, no difference was observed in

mean baseline scores for the NOR group ( $114.60 \pm 69.55$  seconds) compared to the No-NOR group ( $115.80 \pm 68.38$  seconds,  $t=-0.12$ ,  $p=0.547$ ).

We conducted a regression analysis to assess associations between change in HDRS and OQ-45 scores in relation to change in performance on the TMT A and B tests. Change from baseline in time to complete the TMT A and TMT B at discharge does not generally appear to be associated with changes in mood and functioning during inpatient stay as measured by the HAM-D or the OQ-45. Regression coefficients for percent change in TMT A and TMT B scores regressed on percent change in HAM-D were  $-0.08$  ( $p=0.597$ ) for TMT A and  $0.45$  for TMT B ( $p=0.041$ ,  $aR^2=0.033$ ). The comparable regression coefficients for percent change in the OQ-45 were  $-0.06$  ( $p=0.627$ ) for TMT A and  $0.003$  ( $p=0.958$ ) for TMT B. Regressions of TMT A and TMT B on HAM-D and OQ-45 for the subset of subjects with a primary diagnosis of mood disorder were likewise generally not significant and had low  $aR^2$  values. The regression coefficients for TMT A and TMT B on HAM-D were  $0.09$  ( $p=0.577$ ) and  $0.71$  ( $p=0.007$ ,  $aR^2=0.085$ ) respectively, for subjects with mood disorder as the primary diagnosis. The comparable values for regression coefficients operating on the OQ-45 were  $0.05$  ( $p=0.696$ ) for the TMT A and  $0.12$  ( $p=0.581$ ) for the TMT B.

### Discussion

Our study was naturalistic, we accepted patients with various problems and diagnoses in addition to depression complaints. This adds external validity to our results and, as such, they are generalizable to a larger population. The results of the present study show that patients admitted to an inpatient unit experienced dramatic changes in their depression and functioning scores during a relatively short stay. Such findings suggest that most patients admitted to the unit with reportedly very severe depression (HAMD=23.9 on admission) most likely had an adjustment disorder with depressed mood that was connected to some environmental factors in their life, rather than a severe depressive episode. The old definition of adjustment disorder in DSMs IV American Psychiatric Association [24] and DSM 5 American Psychiatric Association [1] is reactive depression. Once the patients were contained on the unit and helped with medications in a supportive therapy milieu, they became only mildly depressed (HAMD=8.6 at discharge). This finding is supported by the 21 points significant drop in Symptoms Distress score on the OQ45 between admission and discharge. The Symptoms Distress score had much more improvement at discharge than the Interpersonal Relationship and Social Role scores, although all three domains of OQ45 improved significantly. This finding adds incremental validity to the improvement of situational depression and relief of distress during an inpatient stays [25]. Other important areas of functioning, such as relationships and social roles, need more time in treatment to achieve substantial improvement [25]. If patients would have had severe major depression, it's unlikely they would have had such a dramatic

improvement in 3-15 days of an inpatient stay [26]. Such dramatic improvement in depression and distress suggests that the short inpatient stay acted as a “holding environment” [26-28] for our patients.

The study showed that those patients receiving medications enhancing norepinephrine improved their cognitive functioning significantly more than those on medications without this mechanism of action. More specifically, patients on norepinephrine-enhancing medications became significantly faster in completing a visual-spatial timed task; their attention, concentration, and planning abilities improved in the process. This finding supports previous research that norepinephrine plays an important role in cognitive functioning [29]. Moreover, norepinephrine-enhancing medications may start exerting their effect on cognition at a faster rate than non-norepinephrine-enhancing medications. For example, in contrast to SSRIs which are characterized by relatively long half-lives (15 hours-15 days) and nonlinear pharmacokinetics, SNRIs-venlafaxine, duloxetine, milnacipran, and desvenlafaxine have relatively short half-lives (5–12 hours) and display linear pharmacokinetics [30]. Thus, SNRIs start to “work faster” on mood and cognition. This finding is also important for treatment adherence purposes. Those patients who start experiencing improvement in mental fastness and unimpeded thinking sooner would be more likely to adhere to the treatment regimen for their depression than those who have to wait 6-8 weeks for SSRIs to work [31]. Also, the improvement in mood could be helpful in improvement in motivation and effort and vice versa.

Our analysis showed that improvement in cognition occurred independently of improvement in depression and functioning scores. This adds support to the direct influence of norepinephrine on cognition. Norepinephrine imbalance is involved in two types of mood-related symptoms: decreased positive affect (i.e., anhedonia, decreased energy, alertness, and self-confidence) and increased negative affect (i.e., guilt, fears, irritability, hostility, and loneliness). Thus, an increase in norepinephrine improves information-processing in brain circuits mediating these symptoms. The brain areas involved in norepinephrine imbalance are the ventro-medial and dorso-lateral prefrontal cortices, amygdala, striatum, nucleus accumbens, and cerebellum. These areas are involved in attention, executive functioning, and motor coordination [32]. All these skills are necessary for completion of the Trail Making Test. Our results show that patients who improved on this test the most are those receiving norepinephrine-enhancing medications. Thus, our study provides evidence that improvement in cognitive performance is one of the main anchors in treatment of depressed mood in the context of different diagnoses. Such cognitive improvement can give patients a “jump start” in pulling themselves out of depression and into the path of functional productivity and enhanced quality of life.

Study limitations include the relatively short period between pre and post-test assessments that could contribute to intrusions during test administration and to some practice effect (although alternative test versions were used).

Future research should include follow-up studies designed to gather data post discharge. For example, assessing patients at 1 and 3 months follow up could shed light on whether the effect of norepinephrine-enhancing medication on cognition persists over time.

## Conclusion

Patients taking SNRIs, alone or in combination with benzodiazepines, Seroquel or TCAs (NOR) had significantly shorter completion times for the TMT A test at discharge than did patients taking SSRIs, with or without benzodiazepines (No-NOR). No differences in mean TMT A scores were found at baseline for the NOR and No-NOR groups. This result was observed for patients with a primary diagnosis of mood disorder as well as for all patients, regardless of diagnosis. The improvement in TMT A was found to be independent from changes in mood (HAM-D scores) and functioning scores (OQ-45).

Mean TMT B scores at baseline and discharge were generally similar for both the NOR and No-NOR patients, regardless of primary diagnosis.

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