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Effect of the Selective Norepinephrine Reuptake Inhibitor Reboxetine on Cognitive Dysfunction in Schizophrenia Patients: An Add-on, Double-Blind Placebo-Controlled Study

Michael Poyurovsky, MD,[1,2] Sarit Faragian, MA,[1] Camil Fuchs, PhD,[3] and Artashez Pashinian, MD,[1]

[1] *Tirat Carmel Mental Health Center, Tirat Carmel, Israel*
[2] *Rappaport Faculty of Medicine, Technion Institute of Technology, Haifa, Israel*
[3] *Department of Statistics and Operations Research, Beverley and Raymond Sackler Faculty of Exact Sciences, Tel Aviv University, Ramat Aviv, Israel*

Abstract: The noradrenergic (NE) system mediates cognitive dysfunction in schizophrenia patients, and the NE transporter represents a putative target for cognitive enhancing therapy. In a double-blind placebo-controlled study we evaluated the effect of add-on reboxetine (4 mg/day), a selective norepinephrine reuptake inhibitor (NRI), co-administered with atypical antipsychotic olanzapine (10 mg/day) on cognitive functioning in DSM-IV schizophrenia patients. The Automated Neuropsychological Assessment Metrics battery and Wisconsin Card Sorting Test were used to assess selective cognitive functions at baseline and endpoint (6 weeks). Clinical assessment was also performed. No between-group differences were found in neurocognitive tests, suggesting that reboxetine did not significantly change patients' cognitive performance compared to placebo. Reboxetine was well-tolerated and did not interfere with the therapeutic effect of olanzapine. Long-term studies using higher reboxetine dosages and alternative NRIs (e.g., atomoxetine) are needed to determine the role of NRIs as cognitive enhancers in patients with schizophrenia and other disorders associated with cognitive impairments.

Introduction

There is increasing evidence indicating that cognitive dysfunction represents an independent symptom dimension associated with functional impairment and reduced quality of life in schizophrenia patients (1). Although currently available antispsychotic agents successfully control positive symptoms of schizophrenia, they have a negligible effect on cognitive symptoms, at best (2). Mechanisms that mediate cognitive dysfunction in schizophrenia have yet to be clarified, nevertheless some neurotransmitter systems and corresponding receptors (e.g., dopamine [DA]-1, NMDA, serotonin [5-HT]-2A, alpha-7 nicotinic receptors) have emerged as putative targets for cognitive enhancement therapy (3, 4).

Several lines of evidence suggest that the noradrenergic (NE) system has marked influence on the prefrontal cortex (PFC) and on cognitive functioning in schizophrenia patients (for review, 5). It has been suggested that NE activation via postsynaptic α-1 adrenergic receptors may have a detrimental effect on working memory (6). In contrast, α-2a adrenergic receptor activation appears to strengthen cognitive function and working memory (7). A cognitive enhancing effect of the α-2a agonists (e.g., guanfacine, clonidine) has been observed in animal models of cognition and in patients with Korsakoff's syndrome, attention deficit hyperactivity disorder and schizophrenia in some but not all studies (5, 8, 9). An additional putative target for cognitive enhancing therapy pertaining to the NE system is the NE transporter (NET, 10). Blockade

Address for Correspondence: Michael Poyurovsky, MD, Director of Research Unit, Tirat Carmel Mental Health Center, POB 9, Tirat Carmel 30200, Israel. E-mail: poyurovs@tx.technion.ac.il

of NET increases extracellular levels of both NE and DA in the PFC, since both neurotransmitters are predominantly taken up from the synaptic cleft by NET owing to a scarcity of dopamine transporters in the PFC (11, 12). Patients with schizophrenia are thought to have a deficit of DA in the PFC which accounts along with other neurotransmitter abnormalities for the cognitive impairment in schizophrenia (13). Overall, these findings led to the suggestion that NET inhibitors by increasing both NE- and DA-dependent PFC-mediated neurocognitive function may improve cognitive impairment in patients with schizophrenia (14).

Reboxetine, a selective norepinephrine reuptake inhibitor (NRI), is broadly used as an antidepressant and anti-anxiety agent. Reboxetine administration was associated with cognitive improvement in healthy volunteers and patients with depression (15, 16). Its addition to antipsychotic agents was safe and well tolerated by patients with schizophrenia (17).

The present study is part of a project aimed to evaluate the effect of reboxetine addition on the clinical and health-related (e.g., weight gain) characteristics of schizophrenia patients treated with atypical antipsychotic olanzapine (18). We hypothesized that reboxetine, owing to its inhibitory effect on the norepinephrine transporter, will ameliorate at least some of the cognitive impairments in olanzapine-treated schizophrenia patients.

Experimental Procedures

Subjects and study design

This study was conducted in Tirat Carmel Mental Health Center (Tirat Carmel, Israel) between October 2003 and October 2006. The study protocol was approved by the Institutional Review Board and was undertaken in accordance with Good Clinical Practice and the provisions of the International Conference on Harmonization, and all patients provided written informed consent after they received a full explanation of the study procedures. All study participants met DSM-IV criteria for schizophrenia or schizophreniform disorder. The diagnosis was based on information obtained from the Structured Clinical Interview for DSM-IV Axis-I Disorders, Patient Edition (SCID-P). Patients with organic brain damage, alcohol / drug abuse or other DSM-IV Axis-I psychiatric disorders were not included. Fifty-nine patients (38 men, 21 women) were randomized for participation in

Table 1. *Demographic and Clinical Characteristics of Patients in the Reboxetine and Placebo Groups*

	Reboxetine (n=16)	Placebo (n=17)		
	Mean (SD)	*Mean (SD)*	*Statistics*	*P*
Age (years)	33.50 (10.60)	28.76 (7.57)	F = 2.20	0.15
Education (years)	11.69 (1.89)	11.82 (2.07)	F = 0.04	0.85
Gender (Male / Female)	10 / 6	11 / 6	χ^2 = 0.02	0.90
Duration of illness (years)	4.23 (5.51)	2.96 (3.46)	F = 0.69	0.63
No. of hospitalizations	1.63 (1.26)	1.47 (0.87)	F = 0.17	0.68
Clinical Rating Scales				
SAPS (total)	11.56 (13.53)	12.29 (10.88)	F = 0.03	0.87
SANS (total)	25.38 (19.79)	23.94 (15.74)	F = 0.05	0.82
CGI	4.31 (0.70)	4.06 (0.56)	F = 1.33	0.26
HAM-D	10.31 (3.34)	10.18 (4.65)	F = 0.01	0.92
SAS	11.31 (2.47)	11.24(2.14)	F = 0.01	0.92
BARS	1.0 (1.03)	0.59(0.80)	F = 1.66	0.21

Table 2. *Speed (milliseconds) and accuracy (percent) of neurocognitive performance before and after treatment in the reboxetine and placebo groups.*

Task	Reboxetine (N=16)		Placebo (N=17)		Group X Time		Effect
	Baseline	Endpoint	Baseline	Endpoint	F(df)	p	size
SRT – *RT*	687.95 (543.83)	450.55 (279.29)	507.19 (198.35)	397.34 (145.74)	0.86 (1, 31)	.36	0.32
Accuracy	99.00 (4.00)	100.0 (0.0)	98.82 (4.85)	100.0 (0.0)	0.88 (1, 31)	.36	0.04
CDS – *RT*	2216.95 (562.82)	1774.12 (408.03)	1918.27 (467.80)	1606.57 (469.82)	1.20 (1,31)	.28	0.38
Accuracy	94.84 (5.09)	95.58 (5.78)	96.61 (3.44)	96.45 (2.36)	0.34 (1, 31)	.56	0.20
CDI – *RT*	2744.44 (1154.12)	1943.70 (882.12)	2252.03 (715.74)	1840.38(574.41)	1.83 (1, 31)	.19	0.47
Accuracy	73.08 (23.82)	81.28 (14.63)	70.99(17.64)	85.31 (13.26)	0.79 (1, 31)	.38	0.31
CDD – *RT*	2144.13 (853.29)	1925.53 (662.15)	1745.93(534.54)	1558.60 (476.78)	0.02 (1, 31)	.90	0.04
Accuracy	70.62 (21.33)	79.09 (11.32)	73.22 (20.04)	81.42 (13.67)	0.01 (1, 31)	.97	0.01
CPT – *RT*	644.44 (128.78)	616.01 (138.29)	672.70 (91.89)	641.16 (73.07)	0.01 (1, 31)	.99	0.01
Accuracy	74.79 (22.87)	79.95 (17.92)	71.35 (23.60)	84.30 (16.31)	0.93 (1,31)	.34	0.34
M2S – *RT*	2245.57 (906.20)	1931.56 (750.45)	1893.79 (783.08)	1741.99 (614.68)	0.35 (1, 31)	.56	0.21
Accuracy	75.99 (19.72)	79.60 (15.89)	84.29 (16.42)	88.64 (17.28)	0.01 (1, 31)	.91	0.04
VSP – *RT*	3963.30 (1492.17)	2984.37 (1532.13)	3629.22 (948.07)	2975.39 (1200.96)	0.66 (1, 31)	.42	0.28
Accuracy	80.94 (17.53)	85.63 (12.50)	84.12 (14.17)	84.12 (13.01)	1.1 (1, 31)	.31	0.33
WCST							
Category	4.50 (2.07)	4.75 (2.02)	4.35 (1.90)	5.00 (1.50)	0.21 (1,31)	0.65	0.16
PSV %	19.56 (13.29)	13.06 (9.74)	20.35 (10.23)	12.06 (8.88)	0.17 (1,31)	0.68	0.15

SRT-Simple Reaction Time; CDS-Code Substitution; CDI-Code Substitution Immediate Recall; CDD-Code Substitution Delayed Recall; CPT-Continuous Performance Test; M2S-Matching to Sample Test; VSP-Visual Spatial Processing; WCST-Wisconsin Card Sorting Test

RT –reaction time

the study. Of these 59 patients, cognitive assessments were available for 33 patients: 10 patients refused to undergo cognitive assessment and the remaining patients did not undergo a second assessment due to technical reasons. There were no differences in socio-demographic or clinical variables between participants (N=33) and those for whom cognitive assessments were not available (N=26). All participants were in a remitted state after a resolution of active psychosis.

Upon entering the study, the participants were randomly allocated in a double-blind design to receive either reboxetine (fixed daily dose of 4 mg/day at 8:00 am; n=16) or identical placebo tablets (at 8:00 am; n=17) co-administered with their primary antipsychotic medication olanzapine (fixed dose of 10 mg at 8:00 pm) for 6 weeks. Prior to the beginning of the study 7 patients in the olanzapine/reboxetine group were drug-naïve, 3 patients received risperidone (2–4 mg/day), 3 patients received haloperidol (5–10 mg/day) and 3 patients received perphenazine (12–16 mg/day). In the olanzapine/placebo group 8 patients were drug-naïve, 4 patients received risperidone (2–4 mg/day), 2 patients received haloperidol (10 mg/day), and 3 patients received perphenazine (8–16 mg/day). The mean duration of antipsychotic treatment prior to the initiation of the study was 6.2 ± 3.1 weeks. Administration of an anticholinergic agent (trihexyphenidyl 5 mg/day; biperiden 2–4mg/day) for extrapyramidal side effects (EPS) and benzodiazepines (lorazepam 1–3 mg/day; diazepam 5mg/day) for insomnia or agitation were allowed on an as-needed basis; no other antipsychotics, antidepressants or mood stabilizers were permitted. The doses of all medications remained unchanged during the entire study period. None of them had abnormal findings on routine physical examination and laboratory tests, including electrocardiography and drug screening, when appropriate.

Clinical ratings

Clinical assessment instruments included the Schedule for the Assessment of Positive (SAPS, 19) and Negative (SANS, 20) Symptoms, the Clinical Global Impression (CGI) scale for the severity of psychosis (21), and the 17-item Hamilton Rating Scale for Depression (HAM-D, 22). Drug-induced EPS were evaluated using the Barnes Akathisia Rating Scale (BARS, 23), the Simpson-Angus Scale (SAS, 24). For the SAS, the sum of 10 of the 11 items (excluding akathisia) was calculated. Other emergent drug-induced side effects were closely monitored and rated weekly as "present" or "absent."

All clinical ratings were completed at baseline and at week 6 (endpoint) by the same trained psychiatrist (A.P.) who was blind to the patients' treatment assignment.

Neuropsychological assessment

Neurocognitive assessments were performed twice, at baseline after the resolution of acute psychosis when patients were cooperative enough to undergo cognitive assessment, and at the end of the 6-week trial. We used the Automated Neuropsychological Assessment Metrics (ANAM) computerized battery, a set of standardized tests that was designed to measure both accuracy (percent of correct responses) and speed (reaction time for the correct responses) of cognitive processing (25). This computerized battery is particularly suitable for repeated measures testing since it generates alternate forms for every administration. The ANAM configuration for the present study included the following tasks in the following order: 1) Simple Reaction Time (SRT); 2) Code Substitution (CDS, derived from the WAIS-R Digit Symbol) – for the assessment of learning ability; 3) Code Substitution Immediate recall (CDI) – visual immediate memory; 4) Mental rotation task – visual-spatial processing (VSP); 5) Matching to sample test (M2S) – visual recognition; 6) Continuous Performance Test (CPT) – sustained attention; 7) Code Substitution Delayed Recall (CDD)- delayed memory. This battery focuses on rather basic components of cognitive performance that is accuracy and reaction time, in domains that appear to be dysfunctional in patients with schizophrenia. We hypothesized that if reboxetine indeed possesses a cognitive-enhancing effect, it would be revealed in these cognitive domains. The Wisconsin Card Sorting Test (WCST) was administered for the assessment of executive function. Neuropsychological assessments were performed by the psychologist (S.F.) who was blind to the subjects' treatment condition and clinical rating scores.

Data analysis

Statistical analysis was carried out using SPSS for Windows 13 (SPSS Inc., Chicago, III). Analysis of variance (ANOVA) and χ^2-test were used, as appropriate, to compare the demographic and clinical characteristics of the two groups. Overall effect of treatment over time in the two groups was assessed by a repeated-measures analysis of variance (ANOVA-RM), one for each dependent variable, with treatment as the between-group factor and time as the within-subject factor. Effect size scores were calculated for both speed and accuracy of performance by subtracting the mean change score of the reboxetine group from the placebo group and dividing it by the pooled standard deviation of the two groups. The magnitude of the effect size for group differences was evaluated. An effect size 0.20–0.49 is small; 0.50–0.79, moderate; and 0.8–1.00, large (26).

Results

Sixteen patients in the olanzapine/ reboxetine group and 17 in the olanzapine/placebo group completed both cognitive assessments. The two groups did not differ in demographic and clinical characteristics and baseline rating scale scores (Table 1). Noteworthy, our study sample included predominantly first-episode schizophrenia patients with limited exposure to antipsychotic drug treatment prior to enrollment.

Neurocognitive effects

Processing speed and accuracy on each task from the ANAM neuropsychological battery at baseline and at the end of the 6-week trial are presented in Table 2. It is of note that ANAM scores at baseline for both groups were substantially lower than reported normative levels obtained using this neurocognitive battery from non-Israeli healthy controls (25). A set of ANOVAs failed to reveal group by time interaction in speed or accuracy of performance in any of the applied neurocognitive tests, indicating that add-on reboxetine did not significantly change patients' cognitive performance compared to placebo. As shown in Table 2, the effect sizes for group differences were also negligible, all in a small range (Cohen's d = 0.01–0.47). Notably, the accuracy of performance on selective neurocognitive tests (CDD, CPT) was even better, although not statistically significant, in the olanzapine/placebo-treated patients than in their olanzapine/reboxetine-treated counterparts. No between-group differences were found in both categories completed or in perseverative errors on the Wisconsin Card Sorting Test (WCST) at the end of the trial (Table 2). Notably, a set of ANOVAs revealed a main time effect in processing speed and accuracy on a majority of the tests, indicating an overall improvement of participants' cognitive performance at the end of the trial.

Table 3. *Clinical Rating Scale Scores* [*mean (SD)*] *in Reboxetine and Placebo Groups*

	Reboxetine (n = 16)		Placebo (n = 17)			
Rating Scales	**Baseline**	**Endpoint**	**Baseline**	**Endpoint**	**Group x time**	
					F(df)	**P**
SAPS	11.56(13.53)	3.13(3.23)	12.29(10.88)	3.47(4.10)	0.03(1,31)	0.87
SANS	25.38(19.79)	12.47(8.75)	23.94(15.74)	10.60(8.02)	0.02(1,31)	0.89
CGI	4.31(0.70)	3.6(0.5)	4.06(0.56)	3.5(0.7)	0.02(1,31)	0.89
HAM-D	10.31(3.34)	4.53(2.00)	10.18(4.65)	3.00(2.00)	0.59(1,31)	0.45
SAS	11.31(2.47)	9.00(0.10)	11.24(2.14)	9.27(0.80)	0.21(1,31)	0.65
BAS	1.0(1.03)	0.0(0.0)	0.59(0.80)	0.19(0.54)	2.05(1,31)	0.16

Treatment effects

A set of repeated measures ANOVAs revealed significant main effect of time, but not treatment by time interactions for SAPS, SANS, CGI and HAM-D rating scores (Table 3), indicating that regardless of reboxetine addition, olanzapine treatment was associated with a significant improvement of positive, negative and depressive symptoms in schizophrenia patients in both groups. Similarly, there was a substantial improvement in EPS ratings, as reflected in the parallel reduction of the SAS and BAS ratings in the two groups without the between-group difference (Table 3).

Reboxetine was well-tolerated. Anticholinergic agents were not required for any of the participants from either group. Benzodiazepines were given to 5 patients in the olanzapine/reboxetine group and 6 in the olanzapine/placebo group.

Discussion

Our hypothesis regarding a putative cognitive enhancing effect of add-on reboxetine, a selective norepinephrine reuptake inhibitor, in schizophrenia patients was not supported by the findings. Reboxetine addition did not affect processing speed or accuracy of neurocognitive performance. In fact, olanzapine/placebo-treated patients performed better than olanzapine/reboxetine-treated patients on selective neurocognitive tests, although not statistically significantly so. Noteworthy, patients in the two groups revealed overall improvement in neurocognitive performance at the end of the study, pointing to a possible practice effect. It was shown that patients with schizophrenia maintained on typical antipsychotic agents generally do not exhibit a practice effect, while treatment with atypical antipsychotics (e.g., olanzapine, risperidone) has been associated with practice-related improvements (27). Finally, reboxetine addition was safe and well-tolerated and did not interfere with the beneficial effect of olanzapine on schizophrenia symptoms and preexisting extrapyramidal side effects.

The major limitations of the present study are the small sample size, short duration of trial, fixed dose of add-on reboxetine and limited number of neurocognitive tests. It is unlikely, however, that the relatively small sample size of the two groups accounted for not detecting a between-group difference (type II error), since not even a minor signal indicating a possible group difference was noted. Interestingly, using the same neurocognitive battery in a smaller sample of chronic schizophrenia patients treated by typical antipsychotic agents, we were able to reveal a potential cognitive-enhancing effect of mianserin, a 5-HT2A/α -2 receptor antagonist (28). The difference in the study population, namely predominantly first-episode patients in the present study versus chronic schizophrenia patients in the mianserin study, may account for our failure to detect reboxetine's cognitive modifying effect. In addition, the tasks included in the ANAM neurocognitive battery administered in this study tap selective cognitive dysfunctions (e.g., learning ability, visual-spatial memory, sustained attention). Supposedly, a more comprehensive cognitive battery, like that recently suggested by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative (29), which includes among others tasks for working memory, verbal memory and social cognition, may be more useful in the detection of a putative cognitive enhancing effect of reboxetine.

Genotyping patients in future research will assist in the evaluation of the effect of reboxetine on cognitive dysfunctions in more homogeneous subgroups of schizophrenia patients. In this respect, the relevant candidate genes are those encoded NET and Catechol-O-Methyltransferase (COMT), the two enzymes involved in catabolism of dopamine and norapinephrine in the PFC (30). It is of note, however, that lack of influence of COMT and NET genes variants on executive functions in schizophrenia patients and their first-degree relatives were also reported (31). The effect of other than reboxetine NET inhibitors (e.g., atomoxetine) on cognitive dysfunctions in schizophrenia patients treated with typical and atypical antipsychotic agents also merits further investigation. The results of such a study have recently been reported and lack of cognitive enhancing effect of atomoxetine was shown, corroborating our findings (32). Finally, agents with combined actions on putative neurotransmitter mechanisms mediating cognitive impairments in schizophrenia, like the 5-HT2A/α-2 receptor antagonist mianserin, may be more promising therapeutic targets for drug development.

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