ORIGINAL RESEARCH

Key Words: PTSD, neuropsychology, paroxetine, memory, short-term, treatment, tests

Neuropsychological Functioning in Patients with Posttraumatic Stress Disorder Following Short-Term Paroxetine Treatment

By Negar Fani, Noriyuki Kitayama, Ali Ashraf, Lai Reed, Nadeem Afzal, Farhan Jawed, J. Douglas Bremner

ABSTRACT ~ *A previous study found improvements in verbal declarative memory in patients with Posttraumatic Stress Disorder (PTSD) following one year of open-label paroxetine treatment. The purpose of the present study was to replicate prior findings and to extend the previous study by comparing the effects of paroxetine versus placebo on cognition in patients with PTSD.* ***Methods****: Eighteen participants with PTSD underwent assessment of neuropsychological function, following which they were randomized to receive controlled-release (CR) paroxetine or placebo, given in a variable dose in a double-blind manner for three months. Neuropsychological testing was then repeated. Subjects who had received placebo were then treated with open-label paroxetine CR and re-assessed.* ***Results****: Paroxetine CR treatment resulted in a significant increase in verbal declarative memory function in the group as a whole, as measured by the Wechsler Memory Scale-Revised, the Selective Reminding Test, and novel paragraph recall, and explicit recall of neutral words. Although we found patterns of improved test performance with paroxetine versus placebo treatment, these differences were not statistically significant.* ***Conclusion****: These findings replicate an earlier finding that open label treatment with paroxetine CR is associated with improvements in verbal declarative memory function. The current study did not show a statistically significant difference between the effects of paroxetine and placebo on memory function, which may in part be related to our small sample size.* Psychopharmacology Bulletin. *2009;42(1):53–68.*

According to the National Comorbidity Survey (1995), posttraumatic stress disorder (PTSD) affects 7.8% of the US population at some time in their lives (10.4% of women, 5% of men).[1] In contrast, a recent study of an urban primary care population found that 34% of participants met diagnostic criteria for lifetime PTSD and 23% met criteria for current PTSD.[2] Clearly, these prevalence estimates indicate that PTSD constitutes a major public health concern.

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Studies have shown that PTSD is associated with lasting changes in neurobiological systems and brain areas that mediate both the stress response and cognition. Extreme psychological stress has been associated with alterations in neurons of the hippocampus, a brain area involved in learning and memory. A number of neuroimaging studies have found smaller hippocampal volume in traumatized individuals with PTSD.[3–7] Functional imaging studies have also shown alterations in brain activity in other regions associated with memory, including the amygdala and medial prefrontal cortex, in patients with PTSD.[40] It has been hypothesized that these changes may, in part, be related to stress-induced alterations in serotonergic function.[8]

Learning and memory impairments are frequently reported in patients with PTSD.[9–12] Verbal memory deficits in particular have been found to be present more often than visual memory deficits,[6,13,14] but some studies show mixed findings. Vasterling and colleagues[15] found that Persian Gulf veterans with PTSD demonstrated more intrusive responses and had deficits in initial and delayed recall as well as retention on a verbal learning task, and worse learning on a visual memory task. In a sample of Vietnam veterans, Bremner and colleagues (1993) found that the PTSD group demonstrated deficits in immediate and delayed recall on verbal, but not figural, subtests of the Wechsler Memory Scale (WMS).[16,17] However, deficits were found in both verbal and visual indices measuring total recall, long-term storage, and long-term retrieval on the Selective Reminding Test (SRT).[18]

Related deficits in attention and executive functioning have been observed in individuals with PTSD. Attentional resources, such as sustained attention, are necessary for proper memory encoding, and some studies have found these abilities to be impaired in participants with PTSD using continuous performance and digit repetition tasks.[15,19] However, these authors did not find that posttraumatic psychopathology was significantly related to poor performance on tasks that required category shifting, such as the Wisconsin Card Sorting Test (WCST),[20] which is consistent with the findings of other investigators.[21] The authors[15,19] did, however, find errors of commission on this task, reflecting decreased ability to respond to irrelevant information, and related this to high symptoms of arousal found in their samples. Some authors[22] have suggested that the neuropsychological impairments found in PTSD are more likely related to premorbidly low intellectual functioning than stress-related neurobiological insult. While Vasterling and colleagues[19] found premorbid estimates of IQ to be significantly lower in veterans with PTSD, scores on intellectual functioning alone did not account for deficits found in sustained attention and learning of verbal material in their sample.

Medications that modulate serotonergic function, including the selective serotonin reuptake inhibitors (SSRIs), have been shown to be efficacious in the treatment of PTSD (for a review, see 23, 41). Paroxetine and sertraline are the two SSRIs approved by the Food and Drug Administration (FDA) as first-line psychopharmacological treatments for PTSD.[24] Paroxetine, specifically, has been shown in two controlled trials to be efficacious in treating clinical symptoms of PTSD,[25,26] and may likewise be useful in improving cognitive function via modulation of serotonergic function in limbic structures, particularly the hippocampus. Animal studies have demonstrated that treatment with SSRIs promotes neurogenesis in the hippocampus.[27] Bartfai et al. (1991) administered clomipramine, which inhibits norepinephrine and serotonin reuptake, for three weeks to subjects with depression[28] and found strong correlations between levels of serotonin metabolites (5-HIAA) found in cerebrospinal fluid and performance on neuropsychological measures. The authors observed a decrease in depressive symptoms and improvements in verbal fluency scores, however, verbal learning and retention was more impaired after treatment.

Although paroxetine has demonstrated effectiveness in the treatment of clinical symptoms of PTSD and depression, only one study to date has examined the effects of paroxetine on cognitive functioning in participants with PTSD.[5] This study found a decrease in PTSD symptomatology in participants following 12 months of open-label treatment with paroxetine, significant improvements in delayed recall and percent retention on logical memory and improved immediate recall for figural memory subtests of the WMS-R. Additionally, participants' performances on verbal and visual memory indices of the SRT were significantly improved with treatment. The purpose of the current study was to replicate the previous open label study and extend it by the addition of a paroxetine-placebo comparison. We hypothesized that paroxetine treatment would be associated with improved performance on measures of verbal declarative memory.

METHODS

Participants

Participants were recruited through fliers and public bulletins. The Investigational Review Board of Emory University approved this study, and all enrolled subjects provided written informed consent. All participants spoke English fluently and had at least an 8th grade reading ability. Participants were considered ineligible if they had experienced significant head trauma or loss of consciousness for at least 10 minutes, or if they reported significant medical histories, current alcohol or

substance abuse or psychotic illness as identified by DSM-IV criteria. All participants had been free from medication for at least one month before data collection. Following phone screening, 64 volunteers completed baseline assessments. Among these, 12 were found ineligible based on not meeting PTSD criterion and 9 were ineligible due to histories of alcohol or drug abuse or dependence, psychotic disorders, or serious medical conditions. Of those who were eligible, 23 discontinued due to medication noncompliance and lack of follow-up. In total, 18 met eligibility criteria (10 women, 8 men) and completed study procedures. Participant demographics and clinical characteristics are described in Table 1. A majority of the participants were right-handed (83%), and slightly more than half were female (56%) and Caucasian (56%), with an average age of 41 years (SD = 9.65 years). Participants reported experiencing frequent and intense PTSD symptomatology over their lifetime; however, reported rates of current PTSD in this sample were moderately high.

Treatment

All enrolled participants were randomized (by an outside researcher) to a 12-week double-blind course of treatment with controlled-release paroxetine or placebo. In this sample, 8 received paroxetine and 10 received placebo during the double-blind phase. Following this 3-month period, participants were notified of their treatment type and those who had received placebo were offered open-label paroxetine for an additional three months. All assessments were repeated after double-blind treatment while subjects were still on study medication, and then again

TABLE 1

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

	MEAN (SD) N = 18
Age	41.44 (9.65)
Gender (female)	55.6%
Race	55.6% Caucasian 44.4% African-American
Years of Education	15.11 (1.91)
Handedness (right)	83.3%
Baseline CAPS Reexperiencing, Current	20.89 (8.63)
CAPS Avoidance, Current	27.56 (12.17)
CAPS Hyperarousal, Current	22.28 (8.91)
Total CAPS Current	70.72 (26.08)
CAPS Reexperiencing Lifetime	25.11 (9.90)
CAPS Avoidance Lifetime	32.94 (10.91)
CAPS Hyperarousal Lifetime	24.22 (9.18)
Total CAPS Lifetime	82.28 (24.33)

at the end of the open label phase. Women received monthly urine pregnancy tests. Study medication was started at one capsule (placebo or paroxetine 12.5 mg) per day. The medication was increased by one capsule (12.5 mg) per study visit, as tolerated by the participant, up to five capsules a day (i.e., 62.5 mg of paroxetine CR). During medication adjustment (i.e., from weeks 0 to 8), subjects were seen biweekly side effect and symptom checks. Subjects then underwent an additional three months of open label treatment, followed by repeat assessment. During weeks 12–24, subjects were seen biweekly for a total of 3 months of open-label treatment. At the end of treatment subjects were either referred for continuing treatment or tapered off of medication.

Measures

Diagnostic and Symptom Severity Measures

The Clinical Administered PTSD Scale (CAPS),[29] a measure with established reliability and validity, was administered to evaluate for presence and severity of both current and lifetime PTSD. The CAPS includes indices measuring re-experiencing, avoidance, and arousal symptoms. All participants who met criterion for current PTSD based on the CAPS were included in this study. Although seven participants had endured multiple life trauma, the most frequently reported primary trauma was childhood sexual abuse (8) followed by adult physical (4) and sexual assault (3), and childhood physical abuse (2), combat (1), and witnessing trauma (1). The Structured Clinical Interview for DSM-IV (SCID)[30] was also used to evaluate possible comorbid diagnoses. In this sample, 13 (72%) met criteria for current major depression and 1 (6%) participant met criteria for past major depression. A number of participants also met criteria for other disorders; seven met criteria for panic disorder (44%), agoraphobia (16%), history of substance abuse or dependence (33%), history of alcohol abuse or dependence (50%), obsessive-compulsive disorder (39%), bipolar disorder (17%), social phobia (11%), specific phobia (22%), or an eating disorder (33%). None of the participants had current alcohol or substance abuse or dependence.

Neuropsychological Assessments

A trained post-doctoral fellow administered a number of neuropsychological assessments to examine potential changes in functioning across several cognitive domains. Trailmaking Tests A and B[31,32] were administered to examine psychomotor speed, attention and executive functioning. For Part A of the Trailmaking Test, examinees are asked to draw a line connecting numbered circles as quickly as possible, while in Part B they are required to alternate between letters and numbers.

Auditory attention and working memory was also measured by the Digit Span subtest of the WAIS-III.[33] WAIS-III Vocabulary and Similarities subtests were administered to measure verbal knowledge and reasoning abilities, while Picture Arrangement and Block Design subtests were used to measure perceptual reasoning and ability to analyze and synthesize abstract visual stimuli. A computerized version of the Wisconsin Card Sorting Test (WCST),[20] a widely used measure of executive functioning, was administered to examine abstract reasoning abilities as well as cognitive flexibility.

Several measures were administered to examine different types (verbal, visual) and stages (encoding, consolidation, retrieval) of memory processes, before and after treatment. Two paragraphs used in the Logical Memory subtest of WMS-R[16] were administered in order to assess memory for contextually-based material. A third novel paragraph was also administered; one of three novel paragraphs was randomly assigned for administration before and after treatment of each participant. Memory for discrete verbal information was assessed through the verbal component of the Selective Reminding Test (SRT). A list of 12 words was read to each participant, and the individual was asked to recall as many words as possible, both immediately and following a delay. All words that are not immediately recalled were selectively presented over 11 subsequent learning trials until the list is recalled in its entirety. The SRT includes indices that measure long-term storage and retrieval mechanisms. A measure of implicit and explicit memory was also administered. First, the examiner presented a series of neutral and emotional words; then, the participant was given a list of word stems to complete that included target words as well as distractor word stems. Following this, the participant was given a page of word stems without distractor to complete.

Memory for discrete visual information was assessed with the visual analog of the Selective Reminding Test; in place of word lists, participants were presented with a series of simple geometric figures for 3 seconds each then were asked to draw all of the figures from memory. The figural memory subtest of the WMS-R[16] was also administered to measure recall of simple visual stimuli both immediately and following a 30 minute delay.

Analyses

A paired-samples t-test was performed to compare pre-treatment and post-treatment performance of all participants (i.e., baseline pre-treatment was compared to a timepoint after treatment with paroxetine, whether during the double blind phase or after open label treatment) on neuropsychological measures; two-tailed tests of significance were used. Significance was defined as $p < 0.05$. A second set of analyses

using a one-way ANOVA was also conducted to compare performance of participants taking paroxetine or placebo following the double blind phase of this study.

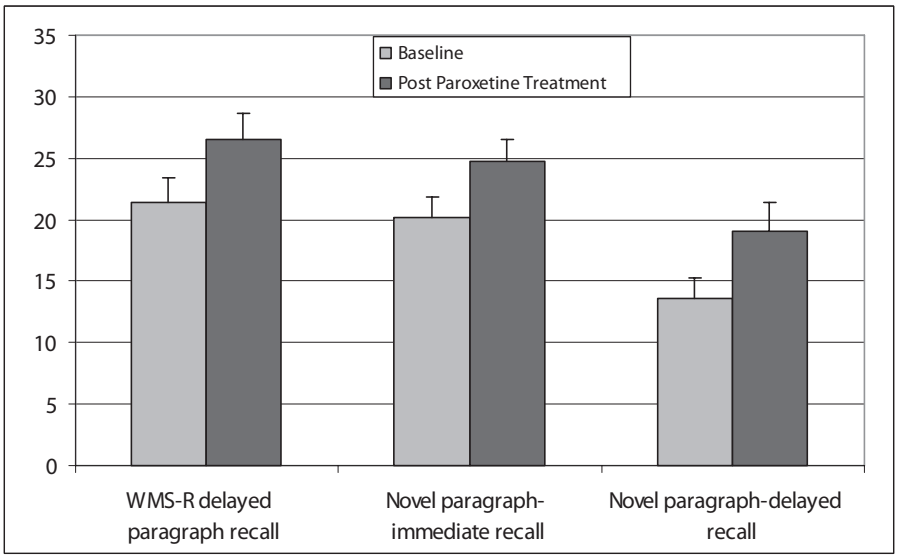
RESULTS

Participants' scores on WAIS-III tests of verbal knowledge [WAIS-III Vocabulary; mean (scaled score) = 10.22, SD = 1.99) and verbal reasoning [WAIS-III Similarities; Mean (scaled score) = 11.56, SD = 3.05] were within average range when compared to a normative sample. On measures of attention and working memory [WAIS-III Digit Span; mean (scaled score) = 11.23, SD = 2.56] and perceptual reasoning [WAIS-III Block Design; mean (scaled score) = 10, SD = 2.06; WAIS-III Picture Arrangement; mean (scaled score) = 11.06, SD = 2.13] participants' scores were also within average range. There were no statistically significant differences for WAIS-III subtest performance between participants taking paroxetine CR and those taking placebo during the double blind phase ($p > 0.05$).

For the rest of the measures, an initial set of analyses compared test performance of all participants at baseline to their performance after receiving 12-week paroxetine CR treatment. Paroxetine treatment in the group as a whole resulted in statistically significant improvements for both immediate (20.1 to 24.8, $p = 0.035$) and delayed (13.6 to 19.1, $p = 0.010$) recall of novel paragraphs (see Figure 1), but not for percent

FIGURE 1

PARAGRAPH RECALL FOLLOWING PAROXETINE TREATMENT



retention, although a trend was evident (66.3 to 78.2, p = 0.069). Participants demonstrated improved delayed recall of the WMS-R paragraphs (21.4–26.5, p = 0.002) but showed no statistically significant changes in immediate recall (27.3–29.5, p = 0.396) or percent retention (78 to 91, p = 0.076). Participants demonstrated improvements on all verbal subscales of the SRT, with the exception of delayed recall (see Table 2).

Paroxetine also resulted in an improvement in figural (i.e., visual) memory as measured with immediate (28.9 to 32.53, p = 0.052) and

TABLE 2

PERFORMANCE ON COGNITIVE MEASURES FOLLOWING PAROXETINE TREATMENT IN POSTTRAUMATIC STRESS DISORDER IN THE GROUP AS A WHOLE (N = 18)

	BASELINE		POSTTREATMENT			
	MEAN	SD	MEAN	SD	T	P
Verbal Knowledge						
WAIS-III Vocabulary	10.22	1.99				
Verbal Reasoning						
WAIS-III Similarities	11.56	3.05				
Attention and Working Memory						
WAIS-III Digit Span	11.23	2.56				
Psychomotor Speed						
Trailmaking Test Part A (sec)	45.71	14.09	42.14	14.97	0.82	0.43
Perceptual Reasoning						
WAIS-III Picture arrangement (scaled score)	11.06	2.13				
Visuoconstructive Ability						
WAIS-III Block Design (scaled score)	10	2.07				
Verbal Learning and Memory						
WMS Logical Memory						
WMS Paragraphs immediate	27.33	8.22	29.53	8.57	−0.875	0.396
WMS Paragraphs delayed	21.4	7.94	26.53	7.99	−3.69	**0.002**
WMS Percent retention	0.78	0.17	0.91	0.18	−1.913	0.076
Novel Paragraph Recall						
Novel paragraph immediate	20.13	6.61	24.8	6.57	−2.32	**0.035**
Novel paragraph delayed	13.6	6.37	19.07	9.02	−2.97	**0.01**
Novel paragraph percent retention	0.66	0.22	0.78	0.31	−1.97	0.069
Selective Reminding Test—Verbal Subtests						
Verbal Total Recall	121.4	15.75	131.07	13.51	−3.86	**0.002**
Long term storage	117.73	19.95	128.67	17.19	−4.39	**0.001**
Long term retrieval	111.87	23.68	126.13	20.28	−4.01	**0.001**
Continuous long term retrieval	94.2	39.49	118.73	31.18	−2.95	**0.01**
Delayed recall	9.8	2.01	10.47	2.77	−1	0.334

(*continued*)

TABLE 2 (*CONTINUED*)

	BASELINE		POSTTREATMENT			
	MEAN	SD	MEAN	SD	T	P
Visual Memory						
WMS Figural Memory						
Immediate recall	28.93	7.73	32.53	5.84	−2.12	0.052
Delayed recall	24.53	10.59	29.33	9.07	−2.13	0.051
Percent retention	82.73	24.47	89.39	20.94	−1.01	0.328
Selective Reminding Test—Visuomotor Subtests						
Total Recall	129.07	16.94	134.53	8.19	−1.81	0.091
Long term storage	127.4	17.92	133.8	9.03	−2	0.066
Long term retrieval	124.93	20.74	132.47	10.25	−1.98	0.068
Continuous long term retrieval	120.07	27.97	127.53	20.56	−1.1	0.292
Delayed retrieval	11.8	0.41	11.33	1.11	1.61	0.131
Implicit Recall and Stem Completion						
Total recall emotional words	3.14	1.66	4.21	2.29	−1.69	0.114
Total recall neutral words	1.64	0.93	1.5	1.45	0.29	0.775
Explicit memory recall emotional	2.57	1.87	3.36	2.27	−1.52	0.151
Explicit memory recall neutral words	1.5	1.99	2.43	2.21	−2.33	**0.037**
Executive Functioning						
Trailmaking Test Part B (sec)	66.5	11.34	69.79	18.91	−0.56	0.585
Wisconsin Card Sort						
Categories Completed	6	0	6	0		
Number of Items	108.33	24.27	94.83	14.24	1.75	0.108
Number Correct	72.75	16.2	72.92	7.97	0.97	0.972
Number of Errors	35.58	24.14	21.92	8.22	1.99	0.072
Number of Perseverative Answers	19.25	10.95	17.75	5.69	0.42	0.682
Number of Perseverative Errors	15.75	8.36	13.08	5.18	1.02	0.33
Number of Nonperseverative Errors	19.75	20.63	8.83	5.31	1.97	0.074
Percent Perseverative Errors	13.67	5.28	13.57	4.24	0.06	0.952
Loss of Set	0.92	1.24	0.83	1.19	0.16	0.878

delayed recall (24.5 to 29.3, p = 0.051) of WMS-R with no effect on percent retention (82.7 to 89.4, p = 0.328). Paroxetine did not result in a significant improvement in visual memory as measured with the visuomotor subtests of the SRT (see Table 2).

Participants demonstrated significantly improved recall of explicit neutral words on a stem completion task following treatment (1.5 to 2.43, p = 0.037), but demonstrated no significant changes in recall of explicit emotional words on the stem completion task. (2.57–3.36, p = 0.151). For the implicit memory stem completion task, paroxetine

treatment showed no effects on stem completion of emotional (3.14–4.21, p = 0.114) words or neutral words (1.6–1.5, p = 0.775).

Treatment resulted in no significant changes in psychomotor speed (Trailmaking Test Part A; t = 0.82, p = 0.427) or in participants' ability to shift cognitive sets (Trailmaking Test Part B; t = −0.56, p = 0.585). With regard to executive functioning, participants demonstrated no significant change in all indices of the WCS (see Table 2). With regard to clinical symptoms, paroxetine CR was associated with a 68% reduction in PTSD symptoms as measured with the CAPS.

A second set of analyses was conducted to compare test performance of participants administered paroxetine (n = 8) and participants administered placebo (n = 10) during the double-blind phase of the study (see Table 3). Participants taking paroxetine during the double-blind phase demonstrated a 24% improvement (21.0–26.1) in delayed recall of WMS-R paragraphs following the double-blind phase, a difference that was statistically significant (t = −2.81, p = 0.026) and placebo participants demonstrated a 16% (21.6–25.1) improvement—this difference was not statistically significant (t = −1.58, p = 0.148; see Figure 2). Direct comparison of paroxetine and placebo groups did not show statistically significant differences (i.e., no treatment group by time interaction) for delayed recall of WMS-R paragraphs (F = 0.299, p = 0.592, η_p^2 = 0.018). Neither group (participants taking paroxetine or placebo) demonstrated significantly improved immediate recall of a novel paragraph after the double-blind phase. Participants taking placebo during the double-blind phase showed significant improvements in delayed recall of a novel paragraph (t = −2.95, p = 0.021), though these changes were not significant for participants taking paroxetine (t = −1.88, p = 0.102).

Participants taking paroxetine during the double-blind phase demonstrated significant improvements in verbal indices of the SRT, including verbal total recall (t = −2.81, p = 0.026), verbal long-term storage (t = −0.2.86, p = 0.024), and verbal long-term recall (t = −2.93, p = 0.022). Participants taking placebo demonstrated no significant improvements on SRT indices, with the exception of long-term storage (t = −2.74, p = 0.023). No significant effects were found in a treatment group by time interaction for these measures, including: verbal total recall (F = 0.035, p = 0.853, η_p^2 = 0.002), verbal long-term storage (F = 0.027, p = 0.873, η_p^2 = 0.002), and verbal long-term recall (F = 0.009, p = 0.928, η_p^2 = 0.001). Participants taking placebo also demonstrated improvement on immediate recall of WMS figures (t = −2.55, p = 0.031); participants taking paroxetine did not show statistically significant improvements on this measure.

There were no other statistically significant differences between paroxetine and placebo groups at the end of the double blind phase for

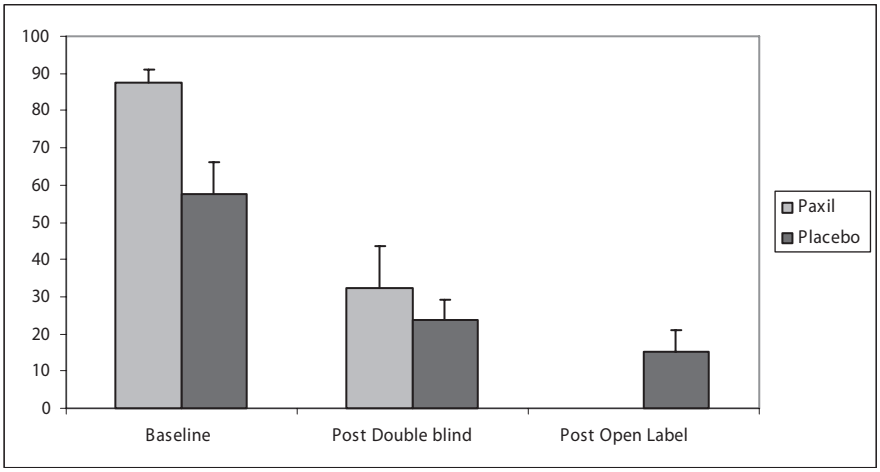
TABLE 3

Cognitive Test Performance and PTSD Symptom Level Before and After Double Blind Administration of Paroxetine or Placebo (N = 18) and Following Open Label Paroxetine in Subjects Administered Placebo During Double Blind Phase (N = 8)

	Baseline Mean (SD)		Following Double-Blind Phase Mean (SD)		Following Open-Label Phase Mean (SD)
Measure	Paxil	Placebo	Paxil	Placebo	Placebo
WMS-R delayed paragraph recall	21 (8.11)	21.6 (8.46)	26.13 (7.36)	25.1 (8.44)	29 (7.74)
Novel paragraph immediate recall	21.25 (7.5)	18.88 (5.30)	25.13 (7.88)	25.13 (5.51)	23.43 (5.38)
Novel paragraph delayed recall	15.38 (6.52)	12.38 (6)	21.25 (7.72)	21.43 (9.07)	19.71 (8.36)
SRT Verbal total recall	128.25 (9.65)	115.7 (15.58)	136.63 (4.31)	123.1 (15.57)	124.71 (17.78)
Long term storage	126.25 (8.78)	111.7 (21.36)	135.88 (4.64)	122.2 (18.32)	120.43 (22.71)
Long term retrieval	122.38 (13.33)	104.2 (24.11)	134.75 (5.39)	115.9 (22.67)	116.29 (26.71)
Continuous long term recall	112 (27.75)	80.6 (39.23)	131.5 (8.8)	100.9 (39.02)	104.14 (41.39)
Verbal delayed recall	10.75 (1.16)	8.1 (2.85)	11.5 (0.93)	9.6 (2.41)	9.29 (3.73)
Explicit recall of neutral words	1.25 (1.49)	1.4 (2.12)	2.29 (1.70)	1.88 (1.36)	2.57 (2.76)
WMS-R Figural immediate recall	32 (4.24)	25.3 (8)	33.5 (3.42)	31.20 (6.07)	31.43 (7.85)
delayed recall	28 (10.03)	21.9 (9.09)	31.88 (3.52)	24.8 (11.09)	26.00 (12.37)
CAPS current Re-experiencing	24.75 (5.63)	17.8 (9.6)	8.38 (7.84)	3.6 (4.65)	3.43 (5.35)
Avoidance	35.63 (7.73)	21.1 (11.37)	13 (15.88)	9.7 (9.39)	5.29 (6.63)
Hyperarousal	27 (6.7)	18.5 (8.91)	10.88 (10.63)	10.4 (7.03)	6.57 (5.29)
Total score	87.38 (10.38)	57.4 (27.52)	32.25 (31.61)	23.7 (17.47)	15.29 (15.14)

FIGURE 2

DECREASE IN TOTAL CAPS SCORE OF PARTICIPANTS TAKING PAROXETINE OR PLACEBEBO FOLLOWING DOUBLE-BLIND AND OPEN LABEL PHASES



all other cognitive measures (see Table 3). This includes explicit recall of neutral words on a stem completion task; however, group by time interaction showed moderate effect size on this task ($F = 1.2$, $p = 0.293$, $\eta_p^2 = 0.085$).

Participants administered paroxetine during the double-blind phase of this study demonstrated a 63.1% reduction in PTSD symptoms as measured by the total CAPS score, a difference that was statistically significant [baseline ($M = 87.38$, $SD = 10.38$) vs. 32.25 (31.61 SD) at the end of double-blind phase ($t = 5.75$, $p = 0.001$), see Figure 2]. Placebo resulted in a 58.7% reduction of symptoms; these participants had a mean CAPS score of 57.4 (27.52 SD), which fell to 23.7 (17.47 SD) following the double-blind phase, also a statistically significant difference ($t = 4.56$, $p = 0.001$). Following open-label paroxetine treatment these participants showed further reductions in CAPS total score [$M = 15.29$(15.14 SD), $t = 4.28$, $p = 0.005$)]. Direct comparison of paroxetine and placebo groups did not show statistically significant differences (i.e., no treatment group by time interaction for total CAPS score; $F = 3.25$, $p = 0.090$); however, effect size for this interaction was moderate ($\eta_p^2 = 0.169$).

DISCUSSION

Paroxetine CR treatment was associated with improvements in verbal declarative memory function when baseline memory performance was compared to post-treatment performance in the group as a whole (i.e., after treatment with paroxetine, whether during the double blind phase or after open label treatment). Paroxetine CR was associated with an

increased ability to encode and recall contextually-relevant verbal information (WMS logical memory delayed recall and novel paragraph recall) as well as discrete orally-presented verbal material (verbal subtests of the SRT and explicit neutral word recall).

The current study showed patterns of improvements in neuropsychological test performance in participants taking paroxetine CR compared to participants taking placebo during the double-blind phase of treatment, although the differences between treatments did not reach statistical significance. Specifically, we found greater improvements in delayed recall of paragraphs, improved long-term and total recall of discretely presented verbal information, and improved recall of explicitly presented, emotionally neutral words. Interestingly, placebo treatment was associated with improved scores on some measures as well, including verbal as well as figural memory indices. Similarly, both paroxetine CR and placebo treatment was associated with decreases in PTSD symptomatology. These differences were not significant; however, effect sizes for the paroxetine-treated group were larger than that of the placebo group.

Findings of improved declarative memory in the group as a whole replicates the findings of Vermetten and colleagues (2003), who also found that 12 months of open-label paroxetine treatment was associated with improved verbal declarative memory in patients with PTSD.[5] Our participants also demonstrated improved performance on an explicit verbal memory task. Paroxetine appeared to have a preferential effect on verbal memory compared to visual memory, although patterns of improved performance were nearly significant for two measures of figural memory. No significant improvements were apparent on measures of attention and executive functioning, which is not surprising given that such impairments have historically shown weak associations with PTSD symptomatology. With regard to intellectual ability (as measured by subtests of the WAIS-III), test performance for this sample of participants was within average range compared to a normative population; this may suggest that the neuropsychological performance of these participants was not limited by premorbid deficits in intellectual ability.

There are several possible explanations for the improvements we observed in verbal declarative memory performance. Paroxetine CR may affect brain regions that mediate memory function via serotonergic mechanisms. Paroxetine inhibits reuptake of serotonin into the neuron. Serotonergic neurons have been linked to dendritic growth in pyramidal cells of the hippocampus and are involved with sympathetic regulation, and alterations in these pathways have been linked to stress-related disorders.[34] Stress-induced elevations in cortisol have an inhibitory effect on 5-HT_{1A} serotonergic receptors in the hippocampus[35,36] which

is associated with a decrease in hippocampal cell proliferation.[37] In animal models of stress, chronic restraint has been associated with decreased binding as well as fewer numbers of 5-HT_{1A} receptors in the hippocampus with associated increases in anxious behavior.[38,39] Likewise, some animal studies have demonstrated that treatment with selective serotonin reuptake inhibitors (SSRIs) promotes hippocampal proliferation.[27] Thus, it is possible that paroxetine is acting through the serotonergic system to promote hippocampal neurogenesis. Given that the hippocampus has an established association with declarative memory, neuronal proliferation in the hippocampus may relate to the improvements in performance that we observed on measures of declarative memory.

These findings have clinical implications. We found some evidence that short term treatment with controlled-release paroxetine is related to improved memory function, specifically, improved recall of explicitly presented verbal material. This may suggest that medical treatment with paroxetine CR could enhance the effects of psychotherapeutic treatment of PTSD, permitting better recall and integration of information presented in therapy with patients' cognitions and behaviors. We did not find evidence that paroxetine treatment is related to other domains of cognition, including attention and executive functioning; a more extensive neuropsychological test battery is needed to show this more conclusively.

There are several important limitations to the present study that warrant consideration. First, we were unable to find significant differences between paroxetine CR and placebo in terms of effects on cognition and clinical symptoms during double-blind treatment; this may, in part, be due to our small sample size, which significantly restricted power for this study. A larger sample size is needed to observe statistically significant differences in neuropsychological function between paroxetine- and placebo-treated groups. Another possible explanation for our findings is a practice effect. Repeated administrations of a memory test can be related to improved test performance, and this cannot be excluded as a possible interpretation of our findings; use of alternate test forms can be used in future research to help address this concern. However, the larger effect sizes we observed for some measures of memory indicate that such improvements in neuropsychological function were detectable with paroxetine CR treatment. It is also possible that paroxetine was associated with improved concentration, which led to improved encoding and thus, recall, of test material. Finally, the duration of treatment for this study was short—longer term treatment may be necessary to observe statistically significant improvements in test performance, as was observed in an earlier 12-month study of paroxetine.[5] Although as

a group, participants demonstrated significantly fewer symptoms of PTSD, particularly avoidance and numbing, following paroxetine treatment, there were no differences between paroxetine and placebo groups in PTSD symptoms during the double blind phase of the study. The current study, however, was not designed to examine the effects of paroxetine on PTSD symptoms, as previous studies have shown that much larger sample sizes would be required to show such an effect.[5,25,26]

Thus, future placebo-controlled studies with larger sample sizes are needed to better elucidate the effects of paroxetine on cognitive function. Similarly, physiological measures, such as MRI and PET methodologies, can be used to correlate changes in cognitive performance with alterations in brain structure and function. Finally, a more extensive battery of neuropsychological tests can clarify paroxetine-related effects on specific stages of information processing, including early-stage attention, executive functioning, and short-term versus long-term recall of verbal and visuospatial materials.✤

ACKNOWLEDGEMENTS

This project was supported by an Investigator Initiated Research Grant from GlaxoSmithKline and NIH R01 MH056120 and K24 MH076955.

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