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Efficacy of Sertraline in Posttraumatic Stress Disorder Secondary to Interpersonal Trauma or Childhood Abuse

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Background. *In posttraumatic stress disorder (PTSD), the nature of the trauma and the age of occurrence may have substantial effects on psychobiological sequelae and treatment response. Interpersonal trauma (physical/sexual assault) and childhood abuse are both prevalent and associated with later PTSD. This analysis was conducted to specifically assess the efficacy of sertraline in the treatment of PTSD secondary to interpersonal trauma or childhood abuse.*
Methods. *395 adult patients with PTSD were randomized to 12-weeks double-blind treatment with flexible dose sertraline (50–200 mg/d) or placebo. Patients with different index traumas were compared in terms of baseline demographic and clinical characteristics, as well as treatment response. Primary efficacy variables included part 2 of the Clinician Administered PTSD Scale (CAPS-2).*
Results. *Interpersonal trauma and childhood abuse were both more common in females than males, and were associated with early age at time of index trauma and longer duration of PTSD, but not with PTSD symptom severity. Sertraline was significantly more effective than placebo on most primary efficacy variables, irrespective of whether patients had experienced interpersonal trauma or childhood abuse.*
Conclusions. *These data demonstrate that sertraline is valuable for the treatment of PTSD, irrespective of whether the precipitating trauma involves interpersonal trauma in general, or childhood abuse in particular.*

Keywords Posttraumatic Stress Disorder, Sertraline, Interpersonal trauma, Childhood abuse

INTRODUCTION

Posttraumatic stress disorder (PTSD) was once conceptualized as a "normal" reaction to an "abnormal" event, but over time it has become clear that it constitutes a psychiatric disorder, characterized by specific symptoms that occur in only a proportion of those exposed to traumatic events (1). Although PTSD was previously considered to be primarily limited to soldiers in combat, it is now recognized as being a common illness in the civilian population. The landmark National Comorbidity Study estimated that more than 50% of the general population (U.S.) had been exposed to trauma, and that the lifetime prevalence of PTSD was 7.8% (2). Although the most prevalent types of trauma were non-interpersonal (witnessing someone being badly injured or killed, being involved in a fire, flood, natural disaster of life-threatening accidents), the types of trauma associated with the highest rates of subsequent development of PTSD were interpersonal trauma (physical/sexual abuse) and childhood abuse. Further studies have demonstrated that childhood abuse in particular is both highly prevalent

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(3) and strongly associated with subsequent short-term and long-term negative effects (4–6).

Recognition of PTSD as a psychiatric disorder has been encouraged by a growing literature demonstrating specific psychobiological dysfunctions and symptom response to particular interventions. It has been established that PTSD is characterized by neurotransmitter and neuroendocrine abnormalities including identifiable changes in the serotonin system (7,8), and that it responds to treatment with particular medications including the selective serotonin reuptake inhibitors (SSRIs) (9). Whether different kinds of traumas are associated with different psychobiological dysfunctions and require different interventions is a question that has been receiving growing attention (4,10).

Interpersonal traumas (physical or sexual assault) and serious accidents may both lead to PTSD, but the former kind of trauma, especially childhood abuse, has been shown to have more pervasive adverse consequences, with more complex comorbid psychopathology (11–13). Early developmental trauma is associated with specific neurobiological sequelae in animal models (14,15), and there is clinical evidence that childhood abuse in particular is associated with unique long-term neurobiological dysfunctions (16,15). Childhood trauma has been reported to have adverse consequences for treatment outcome in PTSD (17,18), including a worse response to the SSRI paroxetine (17).

In this paper, we analyzed two large randomized placebo-controlled trials of the SSRI, sertraline, for the treatment of PTSD (18,19) in order to determine whether pharmacotherapy response differed in patients with or without an index trauma that involved interpersonal trauma in general, and childhood abuse in particular.

METHOD

Clinical Trials

Data from 2 randomized controlled trials of sertraline in PTSD were combined (18,19). Both trials were 12 week, double-blind, flexible-dose, multi-center comparisons of sertraline and placebo in adult outpatients with PTSD. Taken together, 395 subjects were randomized.

Inclusion and exclusion criteria are described elsewhere in detail (18,19). In brief, patients met DSM-III-R criteria for PTSD (20) as determined by part 1 of the Clinician Administered PTSD Scale (CAPS-1) (21), had an illness duration of at least 6 months, and a total score of 50 or more on part 2 of the Clinician Administered PTSD Scale (CAPS-2). Exclusion criteria included current or past psychotic disorder, a primary diagnosis of major depression, alcohol or substance abuse or dependence in the past 6 months, unstable medical disorder, and current use of psychotropic medication or participation in cognitive-behavioral psychotherapy.

Treatment was initiated at 25 mg/d for 1 week, with flexible daily dosing 50 to 200 mg/d thereafter, based on clinical response and tolerability. Primary outcome measures comprised the 17-item total severity score of the CAPS-2, the Impact of Event Scale (IES) (22), the Clinical Global Impression-Severity scale (CGI-S) and the Clinical Global Impression-Improvement scale (CGI-I) (23). These measures, as well as a number of secondary measures, were administered at regular intervals throughout the trials. Additional assessments during the trial included physical examination and electrocardiogram, laboratory investigations, and monitoring of vital signs, adverse effects, compliance, and concomitant medications.

Trauma Subgroups

At baseline, the investigating clinician characterized the index trauma related to PTSD as natural disaster, serious accident/fire/injury, seeing someone hurt or die, being in a war or combat, or physical or sexual assault. In addition, when physical or sexual assault were present, this was characterized as whether or not it involved childhood abuse.

Physical or sexual assault was classified as “interpersonal,” while natural disaster, serious accident/fire/injury, seeing someone hurt or die were classified as “non-interpersonal.” Being in a war of combat was not included in this differentiation, as these traumas might have included both “interpersonal” and “non-interpersonal” traumas.

Statistical Analysis

Patients with different index traumas (interpersonal vs. non-interpersonal trauma, childhood abuse vs. nonchildhood abuse) were compared in terms of demographic characteristics (age, sex), as well as in terms of clinical characteristics (CAPS-2 severity, duration of PTSD, age at time of index trauma) using an analysis of variance model with terms for study and type of trauma, except for sex where the Mantel-Haenzel χ^2 statistic stratified by study was used.

Primary efficacy variables (CAPS-2, IES, CGI-I, and CGI-S) with last observation carried forward) were analyzed using analysis of covariance, with effects of treatment and study in the model, and baseline scores as the covariates. For the CGI-I there is no baseline value, thus an analysis of variance was performed on the end-point score with treatment and study in the model. All statistical tests were 2-sided and performed at the 0.05 level of significance.

Clinical response to treatment was defined as a 30% or greater decrease in the CAPS-2 scores and a CGI-I rating of 1 (very much improved) or 2 (much improved). Analysis of responder rates used a Mantel-Haenzel χ^2 statistic stratified by study.

To determine predictors of response to treatment, a stepwise logistic regression of responder status was undertaken. In addition to treatment and index trauma, demographic (age, sex), and clinical (baseline PTSD severity, age at index trauma baseline) variables were included.

RESULTS

Demographic and Clinical Characteristics

Rates of index traumatic events experienced by subjects differed according to gender; serious accident/fire/injury and being in a war/combat were more common in males, while physical or sexual assault were more common in females (Table 1).

Patients with interpersonal trauma or childhood abuse differed in a number of respects from their respective comparison groups (of non-interpersonal trauma and non-childhood abuse) (Tables 2, 3). Interpersonal trauma and childhood abuse were

Table 1 Distribution of Traumatic Events by Gender and Treatment

	Females		Males		Total	
	Sertraline	Placebo	Sertraline	Placebo	Sertraline	Placebo
Traumatic event	N = 155	N = 144	N = 39	N = 57	N = 194	N = 201
Natural disaster	0%	1%	0%	2%	0%	1%
Serious accident/fire/injury	3%	10%	20%	23%	7%	13%
Seeing someone hurt or die	10%	10%	15%	9%	11%	9%
Being in a war or combat	0%	0%	31%	16%	6%	4%
Physical or sexual assault	72%	72%	13%	37%	62%	62%
Other event	15%	8%	10%	14%	14%	10%

Table 2 Comparison of Baseline Characteristics by Type of Trauma (Interpersonal Trauma vs. Non-Interpersonal Trauma)

	Interpersonal Trauma	Non-Interpersonal Trauma			
	N = 244	N = 82	F	df	p
Age	36.5 (9.5)	40.9 (11.8)	11.97	1,323	.0006
Males/females, %	12/88	40/60	31.293 (chi-square)	1	.001
CAPS-2	75.6 (16.6)	73.3 (16.5)	0.84	1,314	.361
IES	39.0 (14.9)	36.2 (16.6)	2.04	1,314	.155
CGI-S	4.62 (0.80)	4.50 (0.94)	1.13	1,314	.289
Age at traumatic event	14.7 (12.03)	29.9 (15.8)	84.44	1,323	.0001
Duration of illness	13.1 (11.5)	9.0 (11.2)	7.66	1,323	.006
Time since traumatic event	21.9 (14.2)	10.9 (11.8)	39.16	1,323	.0001

CAPS-2 = Clinician Administered Posttraumatic Stress Disorder Scale, part 2. IES = Impact of Event Scale. CGI-S = Clinical Global Impression-Severity scale.

Table 3 Comparison of Baseline Characteristics by Type of Trauma (Childhood Abuse vs. Non-Childhood Abuse) (using SD)

	Childhood Abuse	Non-Childhood Abuse			
	N = 153	N = 242	F	df	p
Age	36.2 (10.2)	39.8 (10.4)	9.80	1,392	.002
Males/females, %	13/87	31/69	16.492 (chi-square)	1	.001
CAPS-2	74.7 (16.4)	74.7 (17.2)	0.00	1,382	.945
IES	37.2 (15.3)	39.0 (15.3)	1.53	1,382	.216
CGI-S	4.58 (0.84)	4.56 (0.85)	0.00	1,382	.959
Age at traumatic event	7.0 (5.7)	28.0 (12.6)	367.43	1,392	.0001
Duration of illness	16.5 (12.3)	9.5 (11.0)	34.83	1,392	.0001
Time since traumatic event	29.2 (11.9)	11.8 (11.4)	212.89	1,392	.0001

CAPS-2 = Clinician Administered Posttraumatic Stress Disorder Scale, part 2. IES = Impact of Event Scale. CGI-S = Clinical Global Impression-Severity scale.

more common in women, and patients with these index traumas were somewhat younger.

Mean age at the time of the traumatic event was 14.7 years in the interpersonal trauma group, and 7.0 years in the childhood abuse group, significantly earlier than in the respective comparison groups (Tables 2, 3). Correspondingly, duration of illness was longer in the interpersonal trauma and childhood abuse groups. However, there was no difference in baseline severity of PTSD symptoms between the groups.

Response to Treatment

A significant difference was found between sertraline and placebo in all of the primary efficacy measures for patients with interpersonal trauma. While the power to detect a difference was lower in the relatively small sample of patients without interpersonal trauma, significant differences between sertraline and placebo continued to be present on the CGI-I and CGI-S (Table 4). Furthermore, there were significantly more responders to sertraline than placebo in both patients with and without interpersonal trauma (Figure 1). This finding was consistent for the a priori response definition (CAPS-2 AND CGI-I responder), and in terms of the separate CGI -I and CAPS- 2 responder definitions, with the exception of CAPS-2 response in patients without interpersonal trauma where the numerical advantage did not meet statistical significance (sertraline, 76% vs. placebo, 55%; p = 0.069).

Similarly, a significant difference was found between sertraline and placebo in all of the primary efficacy measures for patients with childhood abuse. Significant differences between sertraline and placebo remained present for the CGI-I and CGI-S in patients without childhood abuse (Table 5). Furthermore, there were significantly more responders to sertraline than placebo in both patients with and without childhood abuse (Figure 2).

On logistic regression, no interactions between treatment and any of the other variables were found, thus the final model was purely additive. The model demonstrated that treatment with sertraline was significantly predictive of outcome (p = .0001; chi-square = 15.24, df = 1), as was baseline severity of PTSD symptoms (p = .041; chi-square = 4.16, df = 1). Odds ratio (and 95% confidence interval) of response in the sertraline group over that in the placebo group was 2.51 (1.58; 3.99), while that for baseline PTSD symptom severity was 0.99 (0.98; 1.00). Thus, although patients with interpersonal trauma and childhood abuse were more likely to be female, were younger, with early age at time of index trauma and longer duration of PTSD, none of these characteristics predicted differences in treatment response.

Table 4 Adjusted Mean Change from Baseline to Endpoint by Trauma Type (Interpersonal Trauma vs. Non-Interpersonal Trauma) (using SEM)

	Sertraline	Placebo	F	df	p
N					
Interpersonal trauma	N = 118	N = 119			
Non-interpersonal trauma	N = 33	N = 47			
CAPS-2					
Interpersonal trauma	−33.5 (2.2)	−23.1 (2.2)	10.87	1,233	.0011
Non-interpersonal trauma	−33.1 (4.4)	−27.9 (3.7)	0.83	1,76	.364
IES					
Interpersonal trauma	−17.7 (1.3)	−12.5 (1.3)	7.40	1,233	.007
Non-interpersonal trauma	−19.2 (2.5)	−14.8 (2.1)	1.81	1,76	.182
CGI-S					
Interpersonal trauma	−1.21 (.10)	−0.86 (.10)	5.94	1,233	.016
Non-interpersonal trauma	−1.51 (.21)	−0.83 (.17)	6.49	1,76	.013
CGI-I					
Interpersonal trauma	2.44 (.11)	2.93 (.11)	9.36	1,234	.003
Non-interpersonal trauma	2.26 (.20)	2.89 (.17)	5.67	1,77	.020

CAPS-2 = Clinician Administered Posttraumatic Stress Disorder Scale, part 2. IES = Impact of Event Scale. CGI-S = Clinical Global Impression-Severity scale. CGI-I = Clinical Global Impression-Improvement Scale.

DISCUSSION

Early randomized controlled trials of medication for PTSD comprised relatively small studies of combat veterans. More recently, a limited number of large multi-site trials including subjects exposed to a range of different traumas have been undertaken (9). While sertraline, paroxetine, and fluoxetine have proven more effective than placebo in the treatment of non-combat related PTSD, the question of whether these agents are effective in particular subgroups of patients exposed to different kinds of trauma has received little exploration. Using the database that supported the FDA approval of sertraline in PTSD (27), we determined the response patterns in patients with or without an index trauma involving interpersonal trauma or childhood abuse.

Sertraline was effective for the treatment of PTSD, irrespective of whether the index trauma involved interpersonal trauma or childhood abuse. There were significantly more responders to sertraline than placebo in patients with and without interpersonal trauma, and in patients with and without childhood abuse. As expected from previous community studies (2,3), these patient subgroups differed in demographic and clinical features; nevertheless, these features did not predict response to treatment.

The efficacy of a SSRI in PTSD secondary to different index traumas is consistent with previous work on the neurobiology of trauma and pharmacotherapy of PTSD. A range of preclinical and clinical research has documented the role of serotonergic neurocircuitry in early developmental trauma as well as in other severe stressors (14,15). Furthermore, SSRIs have proven effective in a series of studies undertaken in entirely different populations of PTSD patients (9).

The data here conflict with earlier research that found that patients with childhood abuse (17) or combat in Vietnam (24) have a worse response to pharmacotherapy with SSRIs.

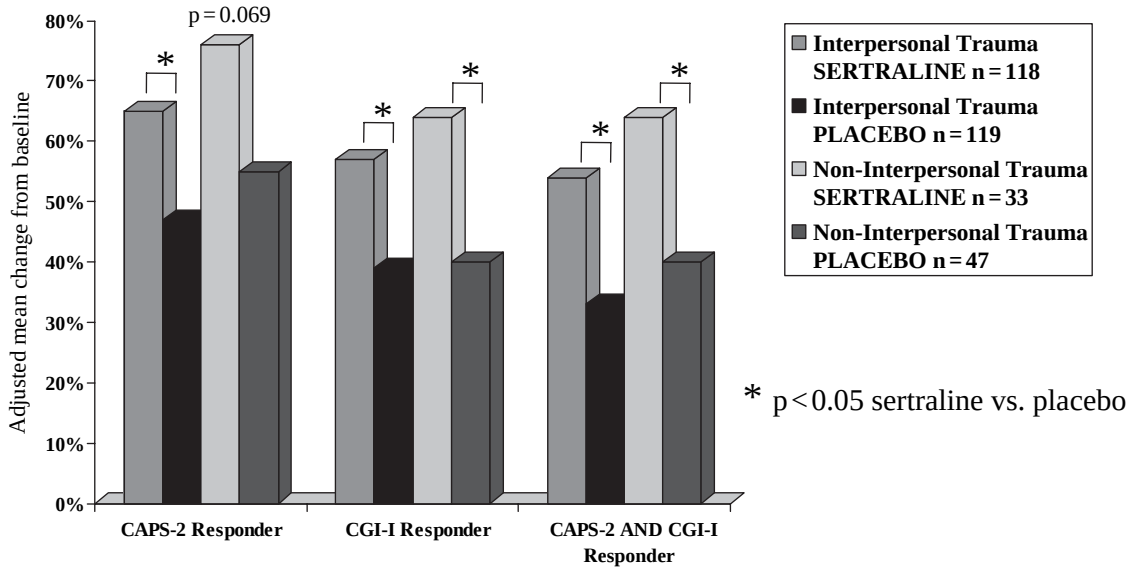

Figure 1 Proportion of Responders at Endpoint By Trauma Type-Interpersonal vs. Non-Interpersonal Trauma CAPS-2 response defined as 30% decrease in baseline CAPS-2 Score, CGI-I response defined as endpoint CGI-I of 1 or 2.

CAPS-2 = Clinician Administered Posttraumatic Stress Disorder Scale, part 2. CGI-I = Clinical Global Impression-Impression scale.

Table 5 Adjusted Mean Change from Baseline to Endpoint by Trauma Type (Childhood Abuse vs. Non-Childhood Abuse) (using SEM)

	Sertraline	Placebo	F	df	p
N					
Childhood abuse	76	77			
Non-childhood abuse	115	117			
CAPS-2					
Childhood abuse	−36.7 (12.8)	−23.4 (2.8)	11.38	1,149	.0001
Non-childhood abuse	−31.4 (2.2)	−25.3 (2.2)	3.68	1,228	.056
IES					
Childhood abuse	−18.7 (1.6)	−12.3 (1.6)	7.89	1,149	.006
Non-childhood abuse	−17.7 (1.4)	−14.4 (1.4)	2.73	1,228	.100
CGI-S					
Childhood abuse	−1.25 (.13)	−0.87 (.13)	4.08,	1,149	.045
Non-childhood abuse	−1.26 (.10)	−0.86 (.10)	7.09	1,228	.008
CGI-I					
Childhood abuse	2.28 (.14)	2.90 (.14)	10.26	1,150	.002
Non-childhood abuse	2.46 (.11)	2.89 (.11)	7.41	1,229	.007

CAPS-2 = Clinician Administered Posttraumatic Stress Disorder Scale, part 2 IES = Impact of Event Scale. CGI-S = Clinical Global Impression-Severity scale. CGI-I = Clinical Global Impression-Improvement scale.

Nevertheless, some of these studies used small numbers of subjects and may not have had sufficient power to exclude type II errors. Alternatively, other characteristics of Vietnam veterans may explain their relatively poor response. Indeed, recent work has found that sertraline is effective in certain combat veterans (25).

It should be emphasized that the current studies were not powered to show significant differences in patients with different index traumas. Furthermore, the complexity of index traumas are not fully explored in these data. For example, PTSD patients may report multiple index traumas, sometimes including both interpersonal and non-interpersonal trauma, or childhood abuse and subsequent trauma (10,26). In addition, a category such as "interpersonal trauma" is not necessarily unambiguous; for example, a serious accident, perhaps classified as "non-interpersonal trauma," may involve the loss of loved ones.

While there have been important advances in our understanding of the neurobiology of early developmental trauma and of PTSD, further work is necessary to delineate fully the correlates and consequences of different kinds of trauma. Further research is also needed to explore whether different index traumas respond differently to pharmacotherapy; in particular it is important to establish to what degree SSRIs not only affect core PTSD symptomatology and comorbidity, but also the more pervasive psychopathology characteristic of complex PTSD after interpersonal trauma or childhood abuse (12,13).

The current data suggest that sertraline is a useful treatment option in PTSD, irrespective of whether the index trauma involves interpersonal trauma or childhood abuse. These traumas are highly prevalent in the community (2,3), and it is therefore important for clinicians to screen for their presence and possible sequelae. Unfortunately, PTSD and other sequelae of interpersonal trauma remain underdiagnosed and undertreated in many settings (4,27). Evidence of the existence of effective treatments for patients with PTSD after interpersonal trauma in general, and childhood abuse in particular, may serve as a useful tool for helping to optimize interventions with traumatized patients.

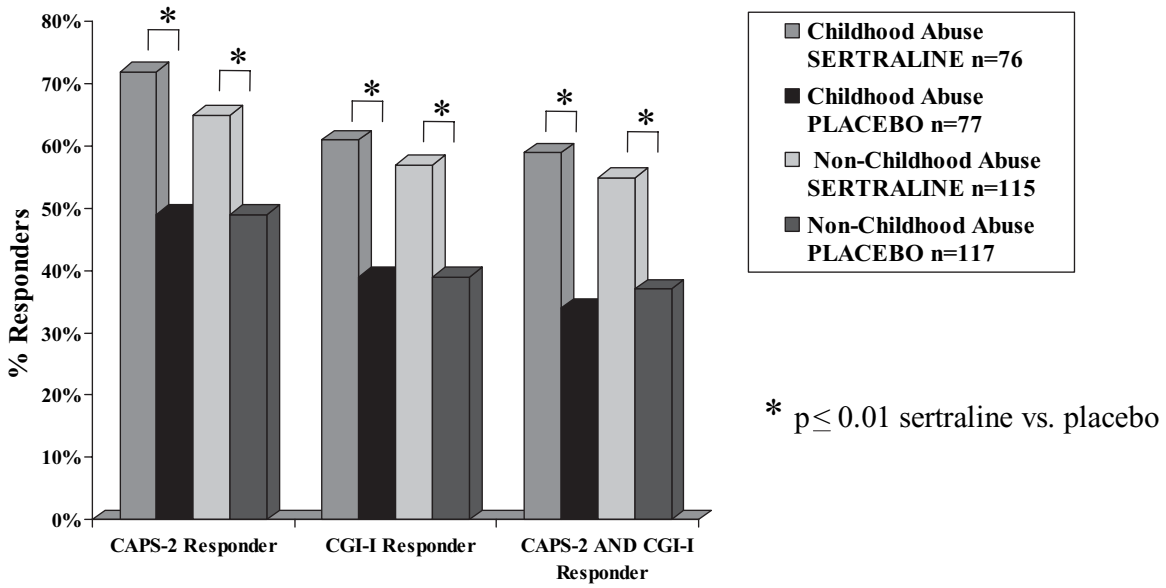

Figure 2 Proportion of Responders at Endpoint By Trauma Type-Childhood Abuse vs. Non-Childhood Abuse CAPS-2 response defined as 30% decrease in baseline CAPS-2 Score, CGI-I response defined as endpoint CGI-I of 1 or 2.

CAPS-2 = Clinician Administered Posttraumatic Stress Disorder Scale, part 2. CGI-I = Clinical Global Impression-Improvement scale.

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