



Decreased suicidal ideation in depressed patients with or without comorbid posttraumatic stress disorder treated with selective serotonin reuptake inhibitors: An open study

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ABSTRACT

Comorbidity of posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) is associated with higher morbidity including suicidal ideation and behavior. Selective serotonin reuptake inhibitors (SSRIs) are a known treatment for PTSD, MDD and comorbid PTSD and MDD. Since the patients with comorbid MDD and PTSD (PTSD–MDD) are sicker, we hypothesize a poorer response to treatment compared to patients with MDD only. Ninety-six MDD patients were included in the study: 76 with MDD only and 20 with PTSD–MDD. Demographic and clinical parameters at baseline were assessed. We examined clinical parameters before and after 3 months of open SSRI treatment in subjects with PTSD–MDD and compared this group to individuals with MDD only. At baseline, PTSD–MDD patients had higher Hamilton Depression Rating Scale and Buss–Durkee Hostility Scale scores compared with MDD only subjects. There was a significant decrease in scores on the Hamilton Depression Rating Scale, Beck Depression Inventory, Beck Hopelessness Scale, and Beck Scale for Suicidal Ideation after 3 months of treatment with SSRIs in both groups. The magnitude of improvement in Beck Scale for Suicidal Ideation scores was greater in the PTSD–MDD group compared to the MDD only subjects. Symptoms of depression including suicidal ideation improved in MDD patients with or without comorbid PTSD after 3 months of treatment with SSRIs but improvement in suicidal ideation was greater in the PTSD–MDD group. Our finding has not supported the hypothesis that a response to treatment is poorer in the PTSD–MDD group which may indicate that sicker patients benefit more from the treatment.

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1. Introduction

Posttraumatic stress disorder (PTSD) occurs following a wide range of extreme life events (APA, 1994; Saigh and Bremner, 1998; Neria et al., 2008; Wittchen et al., 2009). U.S. population surveys reveal lifetime PTSD prevalence rates of 7% to 8% (Keane et al., 2006). According to the National Comorbidity Survey – Replication, the lifetime prevalence of major depressive disorder (MDD) in the United States is 16.6% (Kessler et al., 2005).

Depression and PTSD commonly co-occur (APA, 1994; Bleich et al., 1997; Brown, 2001; Sher, 2005). Significant depressive symptomatology affects 30% to 70% of persons diagnosed with PTSD (APA, 1994; Brown, 2001). Comorbidity of PTSD and MDD is associated with higher morbidity, including suicidal ideation and behavior (Karam et al., 1996; Skodol et al., 1996; Bleich et al., 1997; Oquendo et al., 2003a; Hawgood and De Leo, 2008; Sher, 2009). Symptoms of PTSD and MDD overlap

significantly and the following symptoms are included in both diagnoses: diminished interest or participation in significant activities, irritability, sleep disturbance, and difficulty concentrating. A number of other symptoms are also common in both conditions (e.g., restricted range of affect, detachment from others), thus, the threshold for meeting criteria for both diagnoses is by definition, lower.

Selective serotonin reuptake inhibitors (SSRIs) are widely used for the treatment of MDD, PTSD and comorbid PTSD and MDD. Since the patients with comorbid MDD and PTSD are sicker, they may show a poorer response to treatment compared to patients with MDD only. We have examined clinical parameters before and after three months of open SSRI treatment of comorbid PTSD and MDD (PTSD–MDD) compared with MDD alone. Our hypothesis was that MDD only patients would show a greater degree of improvement with regard to symptoms of depression including suicidal ideation compared to the PTSD–MDD subjects based on a more modest burden of illness.

2. Methods

2.1. Subjects

Participants were recruited through advertising and referrals and participated in mood disorders research in an urban university hospital. After complete description

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Table 1
SSRIs used in the treatment of depressed patients.

Medication	Number of patients treated with this medication	Doses
Paroxetine	47	10–60 mg/day
Citalopram	17	20–80 mg/day
Sertraline	17	50–200 mg/day
Fluoxetine	12	20–60 mg/day
Escitalopram	2	20–80 mg/day
Fluvoxamine	1	50 mg/day

of the study, all subjects gave written informed consent as required by the Institutional Review Board. Ninety-six MDD patients were included in the study: 76 MDD only and 20 PTSD–MDD. The patients were treated openly for 3 months with SSRIs (Table 1). All subjects were free from alcohol or substance use disorder for at least 2 months prior to study entry. The duration of the drug-free status of the subjects was established by a combination of urine and blood toxicological screenings, observation in hospital, and a history obtained from the participant, the participant's family and the referring physician. Patients with psychotic features were excluded. At enrollment, all subjects were free of acute or serious medical illness, based on history, physical examination and laboratory tests, including liver function tests, hematologic profile, thyroid function tests, urinalysis and toxicology.

2.2. Measures

Psychiatric disorders including MDD and PTSD were diagnosed using the Structured Clinical Interview (SCID) for Diagnostic and Statistical Manual of Mental Disorders – fourth edition (DSM-IV) (Spitzer et al., 1996). The following measures were administered at baseline and 3-month follow-up: current severity of depression was assessed by the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and the Beck Depression Inventory (BDI) (Beck et al., 1961), the Scale for Suicide Ideation (SSI) was used to measure the severity of suicidal ideation (Beck et al., 1979), and hopelessness during the previous week was measured with the Beck Hopelessness Scale (BHS) (Beck et al., 1974a).

At baseline, lifetime aggression and impulsivity were assessed with the Aggression History Scale (Brown–Goodwin, revised; Brown and Goodwin, 1986) and the Barratt Impulsivity Scale, respectively (Barratt, 1965). Hostility (lifetime) was rated with the Buss–Durkee Hostility Inventory (Buss and Durkee, 1957). A lifetime history of all suicide attempts, including number of attempts and the method of the attempt, was recorded on the Columbia Suicide History Form (Oquendo et al., 2003b). A suicide attempt was defined as a self-destructive act that was committed with some intent to end one's life. Additionally, the Medical Lethality Rating Scale was used to measure the degree of medical damage caused by each suicide attempt (Beck et al., 1975). The scale was scored from 0 to 8 (0 = no medical damage, 8 = death), with anchor points for different suicide attempt methods. The degree of suicide intent for the worst attempt was rated with the Suicide Intent Scale (Beck et al., 1974b). Interviewers were

Masters or PhD-level psychologists. Inter-rater reliability was good to excellent (ICC 0.71–0.97). A chart review to determine what stressors triggered PTSD in PTSD–MDD subjects was performed by a psychiatrist (L.S.).

2.3. Statistical analysis

Demographic data were compared using Student's *t*-test and chi-square test, as appropriate. Clinical data at baseline and 3 months were compared using paired *t*-test. To evaluate whether a higher prevalence of borderline personality disorder (BPD) was related to the observed higher hostility at baseline in the PTSD–MDD group compared to the MDD group, we fit a regression model with hostility score as the dependent variable and PTSD and BPD diagnoses as predictor variables. To compare the magnitude of changes in the two patient groups, we fit a regression model with the outcome variable (a psychiatric scale score: HDRS, BDI, BHS, or SSI) at 3 months as response variable and the baseline value of the same variable, PTSD diagnosis, and their interaction as predictor variables. SPSS 18.0 program was used to perform statistical analyses.

3. Results

Demographic and clinical characteristics of MDD only and PTSD–MDD groups are presented in Tables 2, 3 and 4. Nine PTSD–MDD subjects experienced trauma leading to PTSD during their childhood, and 11 patients were traumatized during their adulthood. The traumas leading to PTSD in the PTSD–MDD group, as reported by subjects, were as follows: childhood sexual and/or physical abuse ($n=8$); violent crimes ($n=7$) (including rape as an adult ($n=3$) and domestic violence ($n=1$)); witnessing violence and war during childhood ($n=1$); physical injury as a result of an accident ($n=1$); loss of a child as a result of an accident ($n=1$); daughter's rape ($n=1$); and other ($n=1$) (Table 5).

At baseline, PTSD–MDD patients had higher Hamilton Depression Rating Scale and Buss–Durkee Hostility Scale scores compared with the MDD alone group (Tables 3 and 4). There was higher prevalence of BPD in the PTSD–MDD group compared to the MDD patients (Table 2). The regression analysis showed that higher hostility scores in the PTSD–MDD group were attributable to the higher prevalence of subjects with BPD in this group ($F=4.45$, $d.f.=1,91$, $p=0.04$), but not to the PTSD diagnosis ($F=1.94$, $d.f.=1,91$, $p=0.17$).

There was a significant decrease in scores on the Hamilton Depression Rating Scale, Beck Depression Inventory, Beck Hopelessness Scale, and Beck Scale for Suicidal Ideation after 3 months of

Table 2
Demographic and clinical features of depressed subjects with and without a history of posttraumatic stress disorder.

Variable name	Subjects without a history of PTSD ($n=76$)		Subjects with a history of PTSD ($n=20$)		Analysis		
	Mean or (N)	S.D. or (%)	Mean or (N)	S.D. or (%)	d.f.	t/χ^2	p
<i>Demographic features</i>							
Age (yrs)	39.0	12.3	40.9	12.3	94	0.6	0.51
Gender (%males)	(33)	(43.4)	(4)	(20.0)	1	3.7	0.06
Marital status (married)	(16)	(21.1)	(5)	(25.0)	1	0.1	0.69
Education (total years)	15.6	2.9	14.2	3.1	94	–1.9	0.61
<i>Clinical features</i>							
Brown–Goodwin Aggression History Scale	17.7	5.4	18.6	5.2	92	0.6	0.59
Barratt Impulsivity Scale (BIS)	52.7	18.8	50.6	13.3	86	–0.4	0.72
Buss Durkee Hostility Scale	33.7	12.6	40.1	8.6	89	2.0	0.04
Age at first major depressive episode	24.7	13.1	24.1	15.3	92	0.3	0.91
Age at first outpatient psychotherapy	25.7	16.6	33.2	7.9	55	0.1	0.21
Age at first psychiatric hospitalization	31.0	14.0	34.3	8.9	50	0.1	0.53
Number of psychiatric hospitalizations	1.6	3.1	2.1	4.5	83	0.1	0.49
Number of patients with recurrent major depression	(62)	(81.6)	(17)	(85)	1	0.1	0.72
Suicide Attempt status (% attempters)	(27)	(35.5)	(10)	(50)	1	1.4	0.21
Number of suicide attempts (in attempters)	1.9	1.2	2.4	1.6	35	1.1	0.17
Suicide Intent Scale (at the time of the most lethal suicide attempt)	15.0	5.5	15.8	5.7	34	0.4	0.71
Maximum lethality of suicide attempts	2.9	2.0	3.2	2.4	34	0.5	0.68
Smoking status (% smokers)	(17)	(22.4)	(7)	(35)	1	1.4	0.31
Prevalence of borderline personality disorder	(14)	(18.4)	(9)	(45)	1	6.1	0.01
Number of patients who received benzodiazepines or zolpidem	(21)	(27.6)	(8)	(40)	1	1.2	0.28

Table 3

Depression, hopelessness and suicidal ideation scale scores in depressed subjects with and without a history of posttraumatic stress disorder at baseline and after a 3-month treatment with SSRIs (intergroup comparisons).

Variable name	Time point	Subjects without a history of PTSD (n = 76)		Subjects with a history of PTSD (n = 20)		Analysis		
		Mean (Median)	S.D. (IQR) ^a	Mean (Median)	S.D. (IQR) ^a	d.f.	t/z	p
Hamilton Depression Rating Scale (HDRS)	Baseline	24.0	7.8	29.2	9.8	91	2.5	0.01
	3 months treatment	15.1	10.8	17.6	11.8	89	0.9	0.42
Beck Depression Inventory (BDI)	Baseline	25.5	10.7	28.7	11.3	93	0.8	0.41
	3 months treatment	15.3	13.0	15.2	14.4	84	−0.04	0.97
Beck Hopelessness Scale (BHI)	Baseline	11.1	5.7	13.5	5.6	93	1.4	0.19
	3 months treatment	7.6	6.2	8.5	6.9	84	0.6	0.62
Suicide Ideation Scale (SSI)	Baseline	(5)	(14)	(9.5)	(22)		0.9	0.41 ^b
	3 months treatment	(0)	(4)	(1)	(7)		−0.8	0.48 ^b

^a Interquartile range.

^b Mann–Whitney test.

treatment with SSRIs in both patient groups (Tables 3 and 4). However, patients remained significantly depressed.

The regression analysis indicated that the magnitude of improvement with regard to the Beck Scale for Suicidal Ideation was higher in the PTSD–MDD group compared to the MDD only subjects (Table 6). There was no difference in the magnitude of improvement on the Hamilton Depression Rating Scale, Beck Depression Inventory and Beck Hopelessness Scale between the two groups.

4. Discussion

Three months of open SSRI treatment in the comorbid MDD and PTSD group produced more improvement in suicidal ideation compared with patients with MDD only. On measures of depressive symptoms and hopelessness the two groups improved to a similar extent. Our hypothesis, that MDD alone patients would have a better outcome, was not confirmed.

4.1. Baseline comparison

At baseline, the clinician ratings of depression (i.e., HDRS) and hostility were higher in PTSD–MDD compared with MDD alone. Our finding is consistent with previous observations suggesting that PTSD–MDD patients report more severe depression, less social support and more frequent outpatient health care visits compared with MDD-only patients (Campbell et al., 2007). A study of traumatized refugees found that comorbidity of PTSD and MDD was associated with more severe symptoms as well as higher levels of disability on all indices (global dysfunction, distress, social impairment and occupational disability) compared to individuals with PTSD only (Momartin et al., 2004).

The regression analysis indicates that the difference in hostility scores appears to be attributable to the higher prevalence of BPD in

the PTSD–MDD group compared to the MDD only group. We have previously reported that a higher rate of comorbid cluster B personality disorder appears to be a salient factor contributing to greater risk for suicidal acts in PTSD–MDD subjects compared to MDD only (Oquendo et al., 2005). Cluster B personality disorders, particularly borderline personality disorder, are a risk factor for suicidal behavior in depressed patients (Soloff et al., 2000; Kotler et al., 2001; Soloff and Fabio, 2008; McGirr et al., 2009). Borderline personality disorder may have an additive effect with respect to suicidal behavior when it is comorbid with PTSD (Zlotnick et al., 2003). The additional comorbid diagnosis of BPD in patients with PTSD significantly increases the features of suicide proneness and impulsiveness (Zlotnick et al., 2003).

4.2. Clinical parameters after 3 months of treatment

After 3 months of treatment with SSRI, both groups demonstrated significant improvement with regard to both clinician-rated and subjective depression scores, hopelessness scores, and suicidal ideation. The improvement in suicidal ideation was more pronounced in PTSD–MDD subjects compared with the other group. The improvement in depression and hopelessness was comparable in both groups. Our findings may indicate that SSRIs are at least as helpful for patients with PTSD and MDD as for those with MDD only.

Among the antidepressants, the SSRIs are the most commonly prescribed pharmacological intervention for MDD, PTSD and comorbid PTSD and MDD (Ornstein et al., 2000; Stein et al., 2000; Albuchoer and Liberzon, 2002; Rihmer and Akiskal, 2006). The efficacy of SSRIs for the treatment of MDD is well established. Some (van der Kolk et al., 1994; Connor et al., 1999; Brady et al., 2000; Davidson et al., 2001; Marshall et al., 2001; Tucker et al., 2001; Martenyi et al., 2002; Ballenger et al., 2004; Robert et al., 2006) but not all (Friedman et al., 2007) controlled trials also indicate that this class

Table 4

Depression, hopelessness and suicidal ideation scale scores in depressed subjects with and without a history of posttraumatic stress disorder at baseline and after a 3-month treatment with SSRIs (intra-group comparisons).

Variable Name	Group	Baseline		3 month treatment		Analysis		
		Mean (median)	S.D. (IQR) ^a	Mean (median)	S.D. (IQR) ^a	d.f.	t/z	p
Hamilton Depression Rating Scale (HDRS)	Subjects without a history of PTSD	24.0	7.8	15.0	10.8	69	6.7	<0.001
	Subjects with a history of PTSD	29.2	9.8	18.1	11.9	18	4.8	<0.001
Beck Depression Inventory (BDI)	Subjects without a history of PTSD	25.5	10.7	15.0	13.0	64	7.2	<0.001
	Subjects with a history of PTSD	28.7	11.3	15.2	14.4	19	3.7	0.01
Beck Hopelessness Scale (BHI)	Subjects without a history of PTSD	11.1	5.7	7.5	6.1	64	5.1	<0.001
	Subjects with a history of PTSD	13.5	5.6	8.5	6.9	19	3.6	0.02
Suicide Ideation Scale (SSI)	Subjects without a history of PTSD	(5)	(14)	(0)	(4)		−4.4	<0.001 ^b
	Subjects with a history of PTSD	(9.5)	(22)	(1)	(7)		−2.4	0.02 ^b

^a Interquartile range.

^b Wilcoxon test.

Table 5
Experience of trauma and subsequent medical history in depressed patients with posttraumatic stress disorder.

Gender	Age	Traumatic experiences	Recurrence of major depressive episodes	History of suicide attempts (yes/no)	Number of suicide attempts
Female	36	Childhood physical and sexual abuse	Recurrent MDD	Yes	2
Female	44	Childhood sexual abuse	Recurrent MDD	Yes	4
Male	43	Undetermined	Recurrent MDD	Yes	1
Female	22	Rape (adult)	First episode	No	
Female	28	Witnessing violence and war during childhood	Recurrent MDD	Yes	5
Female	31	Childhood sexual abuse	Recurrent MDD	No	
Female	45	Rape (adult)	Recurrent MDD	Yes	1
Female	34	Childhood sexual abuse	Recurrent MDD	Yes	5
Female	51	Childhood sexual abuse	Recurrent MDD	Yes	1
Female	42	Domestic violence (verbal and physical abuse)	First episode	No	
Female	57	Physical assault by armed men (adult)	Recurrent MDD	No	
Male	29	Was shot (adult)	First episode	No	
Female	25	Victim of violent crimes (adolescent and adult)	Recurrent MDD	Yes	2
Male	61	Physical injury as a result of an accident (hit by a car)	Recurrent MDD	No	
Male	64	Loss of son in a car accident	Recurrent MDD	No	
Female	31	Childhood physical abuse	Recurrent MDD	No	
Female	55	Rape (adult), physical assault (adult)	Recurrent MDD	Yes	2
Female	46	Daughter's rape	Recurrent MDD	No	
Female	29	Childhood sexual abuse	Recurrent MDD	No	
Female	44	Childhood sexual abuse	Recurrent MDD	Yes	1

of medications is effective in the treatment of PTSD and its associated problems. Several literature reviews and meta-analyses have recommended SSRIs as first-line treatment for PTSD (Davidson, 2006; Stein et al., 2006). There is limited evidence for the efficacy of SSRIs in the treatment of co-morbid depression and PTSD, and the studies that do exist, are all concerned with co-morbid depression in patients presenting for PTSD treatment. The existing randomized controlled trials show that symptoms of depression are significantly reduced following treatment with SSRIs in PTSD patients regardless of the patient meeting criteria for comorbid major depression or having sub-syndromal symptoms of depression (Davidson, 2006; Stein et al., 2006). Brady et al. (2000) observed significant improvement in symptoms of depression in PTSD patients following treatment with sertraline compared with placebo, and Tucker et al. (2001) reported that paroxetine improved symptoms of depression in a group of patients in treatment for chronic PTSD. Also, Brady and Clary (2003) found that PTSD patients with co-morbid depression responded well to treatment with sertraline, and Stein et al. (2003) found similar results for paroxetine. Regarding patients in treatment for major depression with co-morbid PTSD, little evidence has existed prior to the present study concerning the effectiveness of SSRIs. This underlines the significance of the finding that treatment with SSRI's is comparably effective for depressive symptoms in patients with major depression and comorbid PTSD as in patients with major depression only.

Our study suggests that there is a cause–effect relationship between the baseline HDRS scores and the results, i.e., the improvement is related to the treatment. Although a placebo effect plays a role in the improvement of depressed patients, it is unlikely that such

significant improvement in depressed subjects, especially in depressed patients with comorbid PTSD could be a result of a placebo effect.

This significance of the results is further underlined by the finding that comorbid patients improved more than MDD-only patients on the measure of suicidal ideation. It is that co-morbid group that is at greater risk for suicidal behavior (Oquendo et al., 2003a), and therefore the beneficial effect of SSRIs on suicidal ideation in that group is a particular clinical advantage. A number of studies have found a relationship between PTSD and the risk of suicide among survivors of a variety of traumatic events such as combat trauma (Hendin and Haas, 1991), battered women (Sharhabani-Arzy et al., 2003), sexual abuse (Zlotnick et al., 2001) and rape (Bridgeland et al., 2001). There is evidence that traumatic events such as sexual abuse, combat trauma, rape, and domestic violence generally increase a person's suicide risk (Hendin and Haas, 1991; Bridgeland et al., 2001; Zlotnick et al., 2001; Sharhabani-Arzy et al., 2003). The results of our study are consistent with the observation by Zisook et al. (2009) that decreased suicidality was a function of treatment response.

Improvement of suicidal ideation scores with treatment is clinically important because suicidal ideation predicts suicidal behavior (Fawcett et al., 1990; Beck et al., 1999; Brown et al., 2000; Hatcher-Kay and King, 2003; Galfalvy et al., 2006; Reinherz et al., 2006; Galfalvy et al., 2008). For example, it has been shown that suicidal ideation predicts suicidal acts after major depression in bipolar disorder (Galfalvy et al., 2006).

This is a study of open treatment and needs to be replicated in a randomized placebo controlled clinical trial. Improvement after three months may be related to the natural course of illness or other factors, such as an opportunity to discuss psychological problems with psychiatrists and psychologists-raters. On the other hand, the main objective of the study was to compare MDD with comorbid PTSD to MDD without, and both groups had similar treatment experiences. Another limitation is that the patients were not evaluated using PTSD-specific instruments (such as Clinician-Administered PTSD Scale (CAPS)), i.e., symptoms of depression but not PTSD were evaluated. Other limitations of this study are as follows: a small sample size of the PTSD–MDD group, that since it was as exploratory study, our observation that improvement in suicidal ideation was greater among patients with comorbid PTSD could be chance related to multiple testing.

In summary, our study indicates that the use of SSRIs is associated with improvement in symptoms of depression including suicidal

Table 6

Comparison of the magnitude of changes in depression, hopelessness and suicidal ideation scale scores in depressed subjects with or without a history of posttraumatic stress disorder at baseline and after 3 month treatment with SSRIs.

	d.f.	F	Beta	t	P
Hamilton Depression Rating Scale (HDRS)	1,89	0.6	0.2	0.8	0.4
Beck Depression Inventory (BDI)	1,86	1.5	−0.4	−1.2	0.2
Beck Hopelessness Scale (BHI)	1,85	0.8	0.6	4.8	0.8
Suicide Ideation Scale (SSI)	1,75	4.7	−1.7	−0.8	0.03

A regression model with the outcome variable (a psychiatric scale score: HDRS, BDI, BHS, or SSI) at 3 months as response variable and the baseline value of the same variable, PTSD diagnosis, and their interaction as predictor variables.

ideation in MDD with or without comorbid PTSD. Our finding may indicate that sicker patients benefit more from the treatment. There is a need for further studies of the effectiveness of SSRIs in comorbid PTSD–MDD patients using prospective controlled designs.

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