Triiodothyronine Augmentation of Selective Serotonin Reuptake Inhibitors in Posttraumatic Stress Disorder

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Background: There is considerable comorbidity of major depression and posttraumatic stress disorder (PTSD), and antidepressants have been reported to be effective in treating PTSD. Addition of triiodothyronine (T_3) to ongoing antidepressant treatment is considered an effective augmentation strategy in refractory depression. We report the effect of T_3 augmentation of antidepressants in patients with PTSD.

Method: T_3 (25 μg/day) was added to treatment with a selective serotonin reuptake inhibitor (SSRI) (paroxetine or fluoxetine, 20 mg/day for at least 4 weeks and 40 mg/day for a further 4 weeks) of 5 patients who fulfilled DSM-IV criteria for PTSD but not for major depressive disorder (although all patients had significant depressive symptoms). The Clinician-Administered PTSD Scale, the 21-item Hamilton Rating Scale for Depression, and the Clinical Global Impressions-Severity of Illness scale were administered every 2 weeks, and self-assessments were performed with a 100 mm visual analog mood scale.

Results: In 4 of the 5 patients, partial clinical improvement was observed with SSRI treatment at a daily dose of 20 mg with little further improvement when the dose was raised to 40 mg/day. This improvement was substantially enhanced by the addition of T_3. Improvement was most striking on the Hamilton Rating Scale for Depression.

Conclusion: T_3 augmentation of SSRI treatment may be of therapeutic benefit in patients with PTSD, particularly those with depressive symptoms. Larger samples and controlled studies are needed in order to confirm this observation.

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An extensive literature associates exposure to traumatic events with the co-occurrence of posttraumatic stress disorder (PTSD) and major depression. Major depression was the most prevalent comorbidity with PTSD in 60 Israeli combat veterans (lifetime 95%, current 50%),[1] and high rates (67%) of major depression were also reported by Constans et al.[2] in 260 U.S. veterans with PTSD. Among 211 trauma survivors recruited from a general hospital emergency room, comorbid depression was observed in 44.5% of those who manifested PTSD at 1 month and in 43.2% at 4 months.[3] In the U.S. National Comorbidity Survey, a 48% co-occurrence rate of PTSD and major depression was noted.[4] Breslau et al.[5] found that prior PTSD significantly increased the risk for first-onset major depression (hazards ratio = 2.1) in a random sample of 801 women.

Antidepressant drugs are extensively used in the treatment of PTSD, although their use is supported by a limited number of double-blind, placebo-controlled clinical trials.[6,7] Fluoxetine was evaluated by Van der Kolk et al.[8] in a double-blind study that was completed by 40 patients. PTSD symptoms were significantly improved, including both the arousal and numbing subcategories of the Clinician-Administered PTSD Scale (CAPS). Improvement in depressive symptoms was independent of the effects on PTSD symptoms and was more striking. Brofaromine, a reversible inhibitor of monoamine oxidase type A and a serotonin uptake inhibitor, was not superior to placebo in 2 double-blind studies,[9,10] although in one of the studies[10] there was a significant effect in patients with PTSD of more than 1 year's duration.

Addition of triiodothyronine (T_3) to ongoing antidepressant treatment is considered to be an effective augmentation strategy in patients with refractory depression.[11] In a recent meta-analysis, Aronson et al.[12] aggregated 8 studies, 4 of which were double-blind, placebo-controlled studies, with a total of 292 patients. Patients treated with T_3 augmentation were twice as likely to respond as were controls, a 23.2% absolute improvement in response rates. The effect was not significant when the analysis was limited to the 4 double-blind studies. Almost all published studies have involved addition of T_3 to a tricyclic antidepressant. There are case reports of patients who responded to T_3 augmentation after failing to respond to a selective serotonin reuptake inhibitor (SSRI).[13,14]

Table 1. Scores and Percent Change From Baseline on 4 Rating Scales for 5 Patients With Posttraumatic Stress Disorder[a]

Scale	Baseline Score	SSRI, 20 mg/d (~ 4 weeks) Score	% Change	SSRI, 40 mg/d (~ 8 weeks) Score	% Change	SSRI, 40 mg/d + T_3, 25 μg/d (~ 12 weeks) Score	% Change
CAPS							
Patient 1	49	41	16.3	39	20.4	29	40.8
Patient 2	76	71	6.6	66	13.2	57	25.0
Patient 3	85	63	25.9	61	28.2	48	43.5
Patient 4	80	68	15.0	63	21.3	53	33.8
Patient 5	84	75	10.7	94	11.9	81	3.6
CGI-S							
Patient 1	4	3	25.0	3	25.0	2	50.0
Patient 2	5	4	20.0	4	20.0	3	40.0
Patient 3	5	4	20.0	4	20.0	3	40.0
Patient 4	6	5	16.7	5	16.7	4	33.3
Patient 5	3	3	0	3	0	3	0
HAM-D							
Patient 1	21	17	19.0	15	28.6	10	52.4
Patient 2	23	19	17.4	15	34.8	7	69.6
Patient 3	33	22	33.3	19	42.4	10	69.7
Patient 4	31	26	16.1	25	19.4	13	58.1
Patient 5	20	20	0	22	–10.0	19	5.0
VAS							
Patient 1	25	45	80.0	55	120.0	75	200.0
Patient 2	30	45	50.0	50	66.7	65	116.7
Patient 3	10	25	150.0	25	150.0	50	400.0
Patient 4	10	35	250.0	45	350.0	50	400.0
Patient 5	25	35	40.0	25	0	35	40.0

[a]Abbreviations: CAPS = Clinician-Administered Posttraumatic Stress Disorder Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor, VAS = visual analog scale. Patients 1 and 5 received paroxetine and patients 2–4, fluoxetine.

Since antidepressants have some utility in the treatment of PTSD and a specific effect on depressive components has been reported, it seemed plausible that T_3, an agent that augments antidepressant action in major depression, might do so in PTSD as well. We report 5 patients with chronic PTSD who had significant depressive symptoms but did not fulfill DSM-IV criteria for major depressive disorder. They were treated with SSRIs, which elicited a partial improvement in 4 of them. SSRI treatment was augmented with T_3, and the combination treatment was associated with significant clinical improvement in these 4 patients.

METHOD

All 5 patients were treated in the Hadassah-Hebrew University, Department of Psychiatry Clinic as regular outpatients. None had a history of psychopathology prior to the traumatic event, as determined by clinical history and the Structured Clinical Interview for DSM-IV (SCID).[15] All fulfilled DSM-IV[16] criteria for chronic PTSD. All the patients reported depressive symptoms but none fulfilled DSM-IV criteria for major depressive episode, although they were all very close to the number of criteria required (4 of 5). The patients were free of psychotropic drugs before starting treatment in our clinic, apart from patient 1 who was treated with lorazepam in doses of 1 to 5 mg per week and patient 2 who received clonazepam, 0.5 to 1 mg/day. All the patients were physically healthy, and their plasma thyrotropin levels were within normal limits.

Following an algorithm used in our clinic for the treatment of unipolar major depression (available on request), the patients were first treated with an SSRI (paroxetine in patients 1 and 5 and fluoxetine in the other 3 patients) at a dose of 20 mg/day for at least 4 weeks (mean ± SD = 26 ± 3.7 days) and then at a dose of 40 mg/day for 4 more weeks (mean ± SD = 29 ± 2.3 days). Four patients (patients 1–4) received a benzodiazepine for sleep (brotizolam, 0.25 mg) and 1 (patient 2) also received clonazepam up to 0.5 mg/day. These doses were constant throughout the period of treatment reported here. Since all of the patients were judged to be eligible for augmentation according to the criterion of our algorithm (rating on the Clinical Global Impressions-Improvement scale [CGI-I][17] of minimally improved or worse), augmentation of the SSRI treatment with T_3 (25 μg/day) was then commenced and continued for approximately 4 weeks (mean ± SD = 28.4 ± 0.8 days). Prior to treatment and every 2 weeks during treatment, the patients were administered the following rating instruments (by O.A.): (1) the CAPS,[18] (2) the 21-item Hamilton Rating Scale for Depression (HAM-D),[19] and (3) the CGI.[17] Self-assessments were performed every 2 weeks with a 100-mm visual analog mood scale (VAS).[20]

RESULTS AND CASE VIGNETTES

Scores of the 5 patients on the 4 rating scales are given in Table 1. The following case vignettes summarize the clinical picture and response to treatment of the individual patients:

Patient 1, a 33-year-old male immigrant, had been incarcerated in a Syrian jail for 3 years and tortured. Eighteen months after arrival in Israel, his main symptoms were recurrent, intrusive thoughts and images of the traumatic events he experienced in jail, difficulty staying asleep, distressing dreams, and diminished interest in almost all activities. After 28 days of treatment with paroxetine, 20 mg/day, he reported improvement in his sleep symptoms and distressing dreams, more interest in daily activities, and better concentration. Little further improvement was noted after the paroxetine dose was raised to 40 mg/day for a further 28 days. His improvement was substantially strengthened during the 28 days when paroxetine, 40 mg/day, was augmented with T_3, 25 μg/day. Three months later, his significant improvement

was maintained, and the patient was able to return to work.

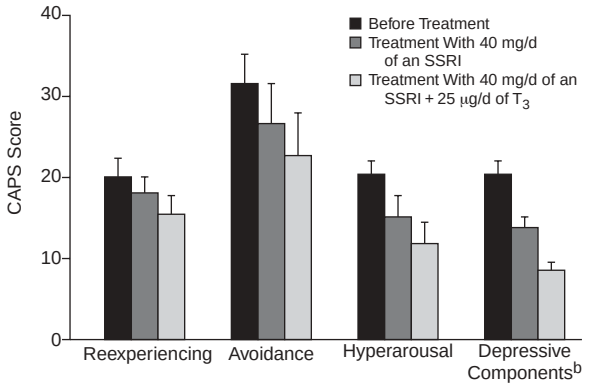
Patient 2, a 47-year-old woman, was hit by a car while crossing a road as a pedestrian. She suffered fractures in both upper and lower limbs. Her psychological symptoms began a few weeks after the accident, and she was treated with clonazepam in doses of 0.5 to 1 mg/day. She presented to our clinic 3 years after the accident with insomnia, anxiety, loss of interest in usual activities, avoidance of places and activities that reminded her of the accident, and difficulty concentrating. Improvement was observed in her avoidance and anxiety symptoms after 25 days of treatment with fluoxetine, 20 mg/day. Minimal further improvement was noted when her fluoxetine dose was raised to 40 mg/day for a further 26 days. Her improvement was magnified after T_3 (25 μg/day) was added to fluoxetine for the next 30 days. Slight deterioration was observed during the next 10 weeks of follow-up, although the overall improvement in her symptoms and functioning was maintained.

Patient 3, a 31-year-old man, witnessed a terrorist bomb attack in the center of Jerusalem. Clinical manifestations of PTSD developed almost immediately, the dominant components being intrusive recollections of the traumatic event, sleep disturbance, distressing dreams, avoidance of places and people, and diminished interest in almost all activities. He began treatment 1 month after the trauma. Fluoxetine, 20 mg/day for 24 days, made him more active and interested in people and improved his sleep. There was little further improvement during the 28 days when the fluoxetine dose was raised to 40 mg/day. Addition of T_3, 25 μg/day, substantially strengthened the improvement of his symptoms over the next 28 days. Five months later, his improvement was maintained.

Patient 4, a 48-year-old man, was involved in an accident while driving a car. He suffered minor physical injuries. His main symptoms were psychological anxiety on exposure to stimuli such as the siren of an ambulance, sudden stops of a car, and sudden noises; severe sleep difficulties; avoidance of almost all activities; and pervasive loss of interest. The symptoms began almost immediately after the accident, 2 months before presenting to our clinic. Improvement in his sleep difficulties and avoidance symptomatology was observed during treatment with fluoxetine, 20 mg/day for 32 days, with minimal further improvement when the fluoxetine dose was raised to 40 mg/day for a further 33 days. Addition of T_3 to fluoxetine resulted in substantial further improvement in his symptoms over the next 28 days. With some initial fluctuation, this improvement has been maintained for 5 months, and he has returned to work.

Patient 5, a 45-year-old woman, witnessed a terrorist bomb attack in the center of Jerusalem. She did not suffer any physical injuries. Clinical manifestations of PTSD developed almost immediately, with intrusive recollections of the event, psychological distress at exposure to sudden noises, severe sleep difficulties, avoidance of contact with others, and loss of interest in all activities. Treatment with paroxetine, 20 mg/day and then 40 mg/day (8 weeks in all), did not change the situation appreciably, nor did the addition of T_3 to the treatment for a further 4 weeks.

Figure 1. Scores of the 4 Patients Who Responded to Treatment on 3 Subscales of the CAPS and on 3 Items of the CAPS Reflecting Depressive Components (mean ± SEM)[a]



[a]Abbreviations: CAPS = Clinician-Administered Posttraumatic Stress Disorder Scale, SSRI = selective serotonin reuptake inhibitor, T_3 = triiodothyronine.
[b]CAPS items 9 (diminished interest or participation in activities), 13 (difficulty falling or staying asleep), and 15 (difficulty concentrating).

As indicated by the individual scores in Table 1, the most striking improvement manifested by the 4 patients who improved on SSRI treatment and experienced further benefit from T_3 augmentation was in symptoms measured by the HAM-D. Improvement of core PTSD symptoms as reflected in CAPS scores was considerably less prominent. We examined the reexperiencing, avoidance, and hyperarousal subscales of the CAPS separately in the 4 responders to treatment (patients 1–4) as well as the items "diminished interest or participation in activities" (item 9), "difficulty falling or staying asleep" (item 13), and "difficulty concentrating" (item 15), which closely approximate items in the HAM-D and which we labeled the CAPS depressive subscale. Improvement on these 4 subscales with SSRI treatment and after T_3 augmentation is shown in Figure 1. It is evident that the most substantial improvement was in the depressive subscale (59.8% with SSRI + T_3 treatment), followed by the hyperarousal subscale (43.2%), with the least improvement on the reexperiencing and avoidance subscales (22.5% in both cases).

COMMENT

The clinical improvement elicited by SSRI treatment in 4 of these 5 patients is in accordance with the findings of controlled studies on the use of antidepressants in the

treatment of PTSD. The 4 patients rated themselves as improved on the VAS, and this overall self-assessment was reflected in the observer-rated CGI-Severity item. Raising the SSRI dose to 40 mg/day for a further 4 weeks added little benefit. Addition of T_3, 25 μg/day, was of substantial benefit to these 4 patients. Overall assessment of clinical state by the VAS and the CGI reflected a doubling of the effect achieved by treatment with the SSRI alone at a dose of 40 mg/day. The effect of T_3 augmentation was evident by 2 weeks. The effect of T_3 in enhancing the clinical response could theoretically have been due to an ongoing action of the SSRI, although this is unlikely after 8 weeks of treatment. Moreover, inspection of the rating scale scores after approximately 4 weeks on treatment with the SSRI, 40 mg/day, showed very little change from the effect seen 2 weeks earlier. Although there was an improvement in CAPS overall scores that ranged from 13.2% to 28.2% on treatment with 40 mg/day of an SSRI and from 25% to 43.5% after augmentation with T_3, improvement of HAM-D scores was more striking (19.4%–42.4% with an SSRI, 40 mg/day; 52.4%–69.7% after augmentation with T_3). Improvement in depressive symptoms (sleep difficulties, diminished interest or participation in activities, and difficulty concentrating) contributed the bulk of the improvement that was seen in overall CAPS scores. This was true for SSRI treatment alone and for SSRI augmentation with T_3. Hyperarousal symptoms were also improved, but symptoms associated with reexperiencing the trauma and avoidance were influenced to a considerably lesser extent.

The positive effects of T_3 in these patients with PTSD could have the same basis as the effect of the hormone in depression. The most intuitive mechanism postulates the existence of hypothyroidism, either clinical or subclinical, in depressed patients. However, most depressed patients are euthyroid, and no consistent relationship exists between basal thyroid hormone levels and responses to T_3.[21,22] Moreover, patients with PTSD have been reported to have increased total T_3, free T_3, and thyroxine (T_4) binding globulin levels.[23–25] An alternative mechanism for the augmenting action of thyroid hormones in depression involves a pharmacologic effect of T_3 on one of the monoamine neurotransmitter systems.[26] Repeated treatment of rats with T_3 led to a decrease in β-adrenergic receptor number and subsensitivity of norepinephrine-induced cyclic adenosine monophosphate formation in rat cortex.[27] Very few studies of the effects of T_3 on brain serotonin (5-HT) levels in animals have been performed. They suggest that T_3 may enhance synaptic availability of 5-HT and alter the sensitivity of 5-HT_{1A} and 5-HT_{1B} receptors.[28,29] Gur et al.[30] substantially extended these studies by applying the in vivo microdialysis technique to examine the effects of T_3 on 5-HT levels in living rat brain. Their findings suggest that T_3 may act by augmenting synaptic availability of serotonin over and above the effect of a concurrently administered antidepressant.

Although T_3 augmentation of antidepressant action in PTSD might be related to the mechanism of action of this hormone in depression, it could also act by a mechanism specific to PTSD. In this regard, it is important to note the studies of Mason and colleagues,[23–25] which assessed thyroid function in combat-related PTSD. Their findings demonstrated an unusual pattern of thyroid alterations, featuring significant elevations in total T_3, free T_3, and T_4 binding globulin levels. The thyrotropin levels of our patients were within normal limits, but we did not have plasma T_3 and T_4 levels, which could have been abnormal even in the presence of a normal thyrotropin level. The mechanism underlying elevation of T_3 levels in patients with PTSD, as reported by Mason et al.,[23–25] is unclear. In the context of elevated T_3 levels, it is paradoxical that exogenous T_3 should elicit symptomatic improvement in PTSD, albeit in depressive rather than core PTSD symptoms. One possibility is that elevated T_3 levels in PTSD may represent a type of chronic arousal response to stress.[31] If this response has adaptive value, exogenous T_3 could contribute further to such an effect.

In conclusion, the cases we have presented demonstrate the potential benefit of T_3 augmentation of SSRI treatment in PTSD. Larger samples and controlled studies are needed to confirm our observations and determine whether they are generalizable to other populations. It also needs to be clarified whether therapeutic benefit from T_3 augmentation is achieved via an effect of the hormone on the depressive component of PTSD or whether other core clinical features of the syndrome are alleviated by the treatment.

Drug names: clonazepam (Klonopin and others), fluoxetine (Prozac), liothyronine (Cytomel, Triostat, and others), lorazepam (Ativan and others), paroxetine (Paxil).

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