Review Paper
Examen critique

Post-traumatic stress disorder and serotonin: new directions for research and treatment

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The overlap in clinical phenomenology and morbidity between post-traumatic stress disorder (PTSD) and such conditions as major depression, anxiety disorders and aggression, in which a serotonin dysfunction is implicated, suggests a role for serotonin in the pathophysiology of PTSD. In this paper, we review current knowledge concerning the role of serotonergic mechanisms and interventions in PTSD. Since there is no clearly effective pharmacologic intervention for this disorder, the underlying neurochemical dysfunction needs to be carefully defined so that more effective treatment can be developed. Preclinical and clinical studies of the serotonergic mechanisms in the pathophysiology of PTSD and treatment trials involving serotonergic agents are limited, but indicate considerable promise. Further investigation of a serotonergic dysfunction in PTSD and of its treatment with serotonergic agents is warranted.

Introduction

Post-traumatic stress disorder (PTSD) is a serious and often devastating chronic mental illness, causing occupational disability, psychiatric and medical morbidity and severe psychosocial distress. The prevalence of PTSD in the general population is estimated to be 7.8%.[1] However, more than one-third of the men and women who served in Vietnam have suffered from this condition during their lifetime.[2] Core symptoms of PTSD include recurrent re-experiencing of the trauma in the form of intrusive memories, nightmares and flashbacks; avoidant behaviours; and autonomic arousal.[3] Patients with PTSD also frequently experience irritability, impulsivity, depression and aggression, in addition to the core PTSD symptoms. Unfortunately, this condition is often difficult to treat.[4]

Over the past 25 years, research efforts have focused on psychologic manifestations of PTSD or the neurobiologic contributions of the hypothalamic–pituitary–adrenal (HPA) axis and noradrenergic dysfunctions. While significant progress has been made

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in understanding the role of catecholamines in the pathophysiology of the disorder, recent initiatives have broadened the scope of the neuroregulation of PTSD to include serotonin. Given the important role of serotonin in depression, anxiety, aggression and the overlap between PTSD with these conditions, one would expect a serotonergic dysfunction in PTSD.

The purpose of this article is to review the role of serotonin in the pathophysiology of PTSD, to review the treatment of PTSD with serotonergic agents and to describe research approaches that show promise in improving our understanding of the neurobiology in patients with PTSD, either combat-induced or occurring in civilian life.

The neuroregulation of PTSD

Current knowledge suggests that there are a variety of complex dysfunctions in multiple neurotransmitter systems in PTSD. Initially, an individual's response to a life-threatening stress involves the immediate and instinctive activation of adaptive "fight-or-flight" mechanisms as a means of survival. This response is behavioural and physiologic, involving a complex cascade of neurochemical and hormonal mechanisms. The HPA axis and catecholamines play a critical role in the modulation of stress, fear, vigilance and cardiovascular responses. Table 1 summarizes the behavioural and neurochemical responses to catastrophic or life-threatening stress, as reviewed by Grillon et al,[5] Charney et al[6] and Southwick et al.[7]

The HPA axis and the norepinephrine system are prominent in most of the biologic research on PTSD. Biologic theories of PTSD have emphasized heightened noradrenergically mediated central responsiveness, as well as altered HPA activity. More recently, a serotonin dysfunction has been implicated in the response to stress and in PTSD.[8,9] The neurotransmitter serotonin influences mood, aggression, arousal, anxiety, sleep, learning, nociception, fear and appetite.[10]

Preclinical and clinical work by Graeff et al[11] suggests that 1) the ascending serotonin pathway, originating in the dorsal raphe nucleus and innervating the amygdala and frontal cortex, facilitates conditioned fear; 2) the dorsal raphe nucleus–periventricular pathway inhibits inborn fight-or-flight reactions to impending danger; and 3) the pathway connecting the median raphe nucleus to the dorsal hippocampus promotes resistance to chronic, unavoidable stress. Additional preclinical evidence, as reviewed by Goddard et al,[12] documents serotonin modulation of norepinephrine function at the level of the locus ceruleus and indicates that serotonin may have an inhibitory effect on norepinephrine neurons. In addition, serotonin terminals from the dorsal raphe and norepinephrine terminals from the locus ceruleus converge on the amygdala to mediate fear responses.

Figure 1 illustrates the neural circuit for fear and the fight-or-flight response, as discussed by Grillon et al,[5] Graeff et al[11] and Goddard et al.[12] It is unclear exactly how the serotonin circuits are disrupted in PTSD.

While no specific neuroimaging studies have fo-

Table 1: The neurochemical correlates of response to catastrophic stressors

Acute response	Neurochemical	Brain regions	Symptoms
Sympathetic activation, "flight" response, fear	Norepinephrine	Locus ceruleus (LC), hippocampus, amygdala, hypothalamus, cerebral cortex	Hypervigilance, autonomic arousal, fear, exaggerated startle response
Conditioning	Norepinephrine	Hippocampus, amygdala, LC, thalamus; bed nucleus of the stria terminalis	Flashbacks, intrusive memories; contextual fear conditioning
Coping strategies, cognitive response	Dopamine	Prefrontal cortex; nucleus accumbens	Paranoia, hallucinations, increased startle response
Analgesia	Opiates	Periaqeductal gray cerebral cortex, amygdala	Lower pain threshold, emotional numbing and withdrawal
Metabolic processes for sustained physical demand and tissue repair	Cortisol	Hypothalamic–pituitary–adrenal (HPA) axis, hippocampus	Vulnerability to physical illness, cognitive deficits
Anxiety	Corticotropin releasing hormone	HPA axis, amygdala, LC, stria terminalis, hippocampus	Free-floating anxiety, increased startle response
"Fight" response, aggressive retaliation, self-defense, rage, resistance to unavoidable stress	Serotonin	Dorsal raphe nucleus, amygdala, frontal cortex, median raphe, hippocampus, hypothalamus	Rage, impulsivity, aggression, violence, suicide attempts, depression, panic, anxiety

cused specifically on the serotonin properties of PTSD, several studies show 1) reduced hippocampal volume in patients with combat-induced and abuse-related PTSD by magnetic resonance imaging,[13,14] which is associated with functional deficits in verbal memory; 2) significant differences from normal in brain metabolic response to yohimbine in patents with combat-induced PTSD in prefrontal, temporal, parietal and orbitofrontal cortexes by positron emission tomography (PET);[15] and 3) increased regional cerebral blood flow in the ventral anterior cingulate gyrus and right amygdala in patients with combat-induced PTSD who generated mental images of combat.[16] These studies document the involvement of the hippocampal, noradrenergic and limbic systems in PTSD. Mann et al[17] found increases in brain metabolism by PET in healthy subjects, but not in depressed patients, in the left prefrontal and temporoparietal cortex after administration of the serotonin-releasing drug d,l-fenfluramine. A similar PET study during serotonin challenge in patients with PTSD may reveal more precisely the brain regions involved in PTSD.

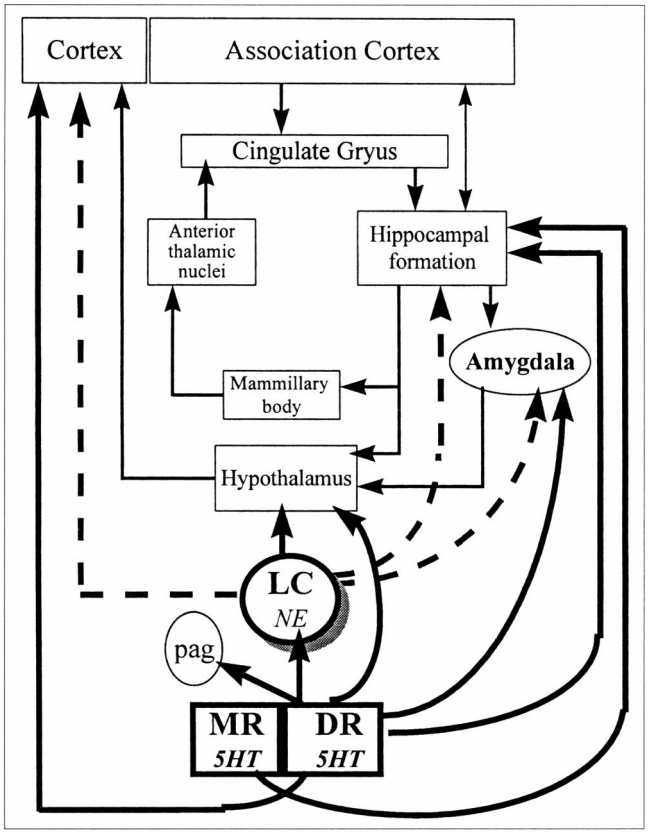

Fig. 1: The neural circuit for fear, with emphasis on the norepinephrine and serotonin pathways (synthesized from theoretical models[5,11,12]). LC = locus ceruleus; NE = norepinephrine; pag = periaqueductal grey; MR = median raphe nucleus, DR = dorsal raphe nucleus; 5HT = serotonin.

PTSD and comorbid conditions involving serotonergic dysfunction

Substantial indirect evidence suggests that a serotonin dysfunction is an important link in the pathophysiology of trauma-related symptoms associated with PTSD. In humans, a dysregulation of serotonin has been associated with depression, anxiety, aggression, impulsivity and suicidal behaviour — all of which are frequently found in patients with PTSD. Figure 2 shows the overlap of PTSD with depression, anxiety/panic and aggression/impulsivity. Major depressive disorder has a lifetime comorbidity of 70% in patients with PTSD.[1,18] Obsessive–compulsive disorder and panic disorder are less frequent comorbid conditions (occurring in 5% and 12 % of patients with PTSD, respectively). There is extensive evidence to support a serotonergic component in the pathophysiology of these illnesses.[12,19]

Antisocial and borderline personality disorders have also been shown to involve serotonergic dysregulation.[20,21] These disorders are also comorbid and complicating factors in patients with PTSD. The lifetime preva-

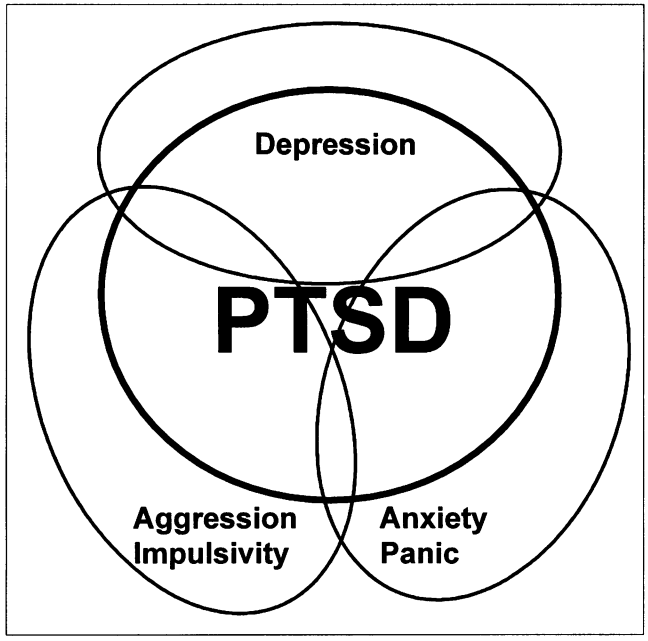

Fig. 2: PTSD and its overlap with depression, anxiety/panic and aggression/impulsivity.

lence of antisocial personality disorder in patients with PTSD is 12%.[18] To meet the criteria for antisocial personality disorder in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), the patient must exhibit antisocial behaviour of juvenile onset, i.e., antisocial behavior since age 15 with conduct disorder before age 15. However, many patients with PTSD have adult-onset and possibly PTSD-linked aggressive and antisocial behaviour, without having had antisocial personality disorder of juvenile onset.

Borderline personality disorder (BPD) is somewhat more complicated. While veterans with combat-induced PTSD have a 12% lifetime prevalence of BPD, only 4% of veterans without PTSD have BPD.[18] Southwick et al[22] evaluated male combat veterans with PTSD using the Personality Disorder Examination and found that 76% (26 of 34 patients) of the total patient group had BPD. Further analysis showed that 83% of the inpatients (15 of 18) had BPD, whereas 69% of the outpatients (11 of 16) had BPD. The difference in clinical populations may account for some of the discrepancy between these 2 studies.

Up to 80% of patients with borderline personality disorder have a history of childhood sexual or physical abuse, and one-third of such patients meet the diagnostic criteria for PTSD.[23] There is extensive interweaving of PTSD and BPD symptoms, and many features of BPD resemble PTSD. The overlap is even more pronounced in women who have experienced sexual assault and have PTSD. The long-term stability of the diagnosis of BPD in a patient with PTSD has not been established. In other words, do the symptoms of BPD resolve as the PTSD is treated? The question of whether BPD is a vulnerability factor or a chronic type of PTSD is pervasive in the literature.[22]

While symptoms of aggression and rage are not required for a DSM-IV diagnosis of PTSD, they are frequent complaints of patients with PTSD. Lasko et al[24] found significantly higher levels of self-reported aggression and hostility in Vietnam combat veterans with PTSD than in combat veterans without PTSD. The group differences were not explained by combat exposure; this suggests that increased aggression in veterans is a property of PTSD, rather than a direct consequence of combat exposure. In fact, the aggression measures in combat veterans without PTSD were similar to those in the comparison group of people who had not experienced combat. In the National Vietnam Veterans Readjustment Study,[2] men with combat-induced PTSD had committed an average of 13.3 acts of violence in the preceding year, compared with 3.5 acts among those without PTSD. Again, the discrepancy between groups could not fully be accounted for by a greater combat exposure in the veterans with PTSD. The number of acts of violence committed by female veterans with PTSD and without PTSD did not differ significantly.

The question of whether premorbid aggression is a vulnerability factor for PTSD was examined by Hiley-Young et al.[25] Of 177 veterans with combat-induced PTSD, more than 30% had suffered physical abuse or exhibited antisocial behaviours during childhood, and 92% of these 177 sujects either participated in or witnessed extreme violence during combat. More than 70% of these patients with PTSD reported acts of violence occurring after military service to others. However, childhood victimization or aggression did not predict war-zone violence or criminal behaviour or violence against others in later life. This study supports the relation of PTSD to subsequent adult aggression, independent of exposure to violence before the traumatic incident.

In animal studies, there is evidence of a direct relation between serotonin levels and aggression. Recently, Higley et al[26] demonstrated that cerebrospinal fluid (CSF) serotonin metabolite (5-HIAA) concentrations were negatively correlated with impulsive behaviour and severe unrestrained aggression in non-human primates. Several studies have found that serotonin-depleting agents increase aggression in rats,[26,27] while this behaviour is decreased by serotonin precursors or agonists.[28]

As with animal studies, the evidence of serotonin dysfunction in individuals with aggressive behaviour is well established. Low CSF 5-HIAA concentrations have been associated with violent criminal behaviour, impulsivity, suicidal behaviour and aggressive behaviours in humans.[30-33] Tryptophan depletion also significantly increases aggressive responses in healthy males.[34] Handelsman et al[35] found that the prolactin response to the partial serotonin agonist meta-chlorophenylpiperazine (MCPP) was inversely associated with measures of hostility, irritability and depression in abstinent alcoholics — again demonstrating a possible relation between serotonin dysfunction and hostility.

Serotonin and PTSD

Several studies have directly examined serotonin func-

tion in patients with PTSD. Arora et al[36] found that the density of platelet serotonin-uptake sites, as determined by paroxetine binding, was significantly decreased in patients with PTSD, compared with normal controls. Interestingly, there was no difference in the paroxetine binding between PTSD patients and those without a diagnosis of major depression. These findings were later extended to a larger sample of patients with PTSD.[37] Again, platelet paroxetine binding did not differ as a function of comorbid major depression, other anxiety disorders or substance abuse. Furthermore, patients with PTSD who were maximal responders to fluoxetine had lower pretreatment paroxetine platelet binding.[38] Conversely, Mellman and Kumar[39] did not find a difference in platelet serotonin concentration and uptake measures between patients with PTSD and normal controls. However, their findings do not rule out a central serotonergic dysfunction that is not reflected in platelet measures.

Southwick et al[8] examined the behavioural effects of MCPP in 14 veterans with combat-induced PTSD. Although no patient had a panic attack and only 1 patient had a flashback following placebo infusion, approximately one-third of the patients had a panic attack and flashbacks after receiving MCPP. This study indicates that there is a subgroup of patients with PTSD who exhibit a behavioural sensitivity to serotonergic provocation.

Treatment of PTSD with serotonergic agents

Several excellent literature reviews on alternative psychopharmacologic treatments for PTSD have concluded that tricyclic antidepressants lead to modest improvement in intrusive re-experiencing symptoms but typically little effect on avoidant or hyperarousal symptoms.[9,40–42] Monoamine oxidase inhibitors appear to be more effective than tricyclics, but show the same spectrum of action. The benzodiazepines, alprazolam and clonazepam, seem to reduce general anxiety symptoms, but show no conclusive actions on core PTSD symptoms. Taken as a whole, few controlled trials have been done with these agents, and few drugs have been tested more than once.

Recently, a number of studies have suggested a promising and possibly unique role for serotonergic treatment for patients with PTSD. Table 2 lists the pharmacologic treatment trials with agents that are primarily serotonergic. In addition to their antidepressant effects, these drugs are effective in improving irritability, impulsivity, aggression and the core symptoms of PTSD.[41]

Among these drugs, fluoxetine has the most published data on its use in the treatment of PTSD and was used in the only controlled trial of a selective serotonin reuptake inhibitor (SSRI) for PTSD. Van der Kolk et al[43] entered 64 subjects with PTSD in a randomized double-blind trial comparing fluoxetine with placebo. Fluoxetine, but not placebo, significantly reduced overall PTSD symptoms, with the reduction of numbing and arousal being the most significant. Interestingly, improvement in depression did not predict improvement in PTSD symptoms. Both acute trauma-induced PTSD in civilians and chronic combat-induced PTSD were studied. When patients were divided by type of trauma exposure, the veterans did poorly compared with the civilians. This result may have been due to the short length of the trial (5 weeks compared with 8 or 10 weeks in other studies) or the chronic nature of PTSD in the veterans compared with the acute PTSD experienced by the civilians. It is noteworthy that patients taking the placebo had almost no change, indicating a very low placebo response in patients with PTSD.

Open trials of fluoxetine[44–48] have demonstrated moderate to marked improvement in both combat-induced PTSD and PTSD occurring in civilian life in approximately 67% of patients. One study also demonstrated a significant reduction in aggression in patients with PTSD taking fluoxetine.[47]

A 10-week open trial of another SSRI, fluvoxamine, in male Vietnam combat veterans with chronic PTSD demonstrated significant improvement in depression, anxiety and the core symptoms of PTSD, while the ratings of hostility showed a modest decline.[49] De Boer et al[50] demonstrated significant, but more modest, therapeutic effects of fluvoxamine in an open-label 12-week treatment of Dutch World War II veterans with chronic PTSD.

Open trials of sertraline[51–53] showed a response rate of 57% to 63% in patients with PTSD. One open trial of clomipramine, a tricyclic with primary serotonergic activity, in patients with PTSD and symptoms of obsessive–compulsive disorder showed a marked reduction in the intrusive symptoms of PTSD and in the obsession scores in 6 of 7 patients.[54] The 5-HT1A partial agonist buspirone has shown benefits in treating the

symptoms of PTSD in an open trial[55] and in case reports.[56,57] In contrast to the SSRIs, however, improvement in avoidant/numbing symptoms of PTSD was not noted with buspirone.

Given the complex interactions among neurotransmitter systems, it is unlikely that changes in any single neurotransmitter are solely responsible for symptoms of a disorder such as PTSD or for the improvement with pharmacologic treatment. Paralleling the theory on the mechanism of action of SSRIs in panic disorder by Goddard et al[12] is the hypothesis that the therapeutic effect of SSRIs in PTSD may be due to an increase in the inhibitory effects of serotonin on norepinephrine in the locus ceruleus, which decrease the hyperarousal, hypervigilance, fear and intrusive memories experienced by patients with PTSD.

The studies we reviewed suggest that controlled trials with serotonergic agents are worth pursuing in patients with PTSD. SSRIs appear to treat specific core symptoms of PTSD to a greater extent than tricylic antidepressants, monoamine oxidase inhibitors or benzodiazepines. However, nonspecific effects of all

Table 2: Studies of treatment of post-traumatic stress disorder (PTSD) with serotonergic medication

Author	No. of patients	Medication	Type of study	Length	Dosage	Outcome
Van der Kolk et al 1994[43]	64	Fluoxetine	Randomized double-blind placebo-controlled	5 wk	20–60 mg/d	Significant reduction in symptoms of patients treated with fluoxetine, but not placebo
McDougle et al 1991[44]	20	Fluoxetine	Open trial	10 wk	20–80 mg/d	Significant improvement in intrusive avoidant and arousal symptoms in 13 of 20 patients
Nagy et al 1993[45]	19	Fluoxetine	Open trial	10 wk	20–80 mg/d	Significant improvement in depression/anxiety, re-experiencing symptoms, avoidance/numbing and hyperarousal symptoms
March 1992[46]	1	Fluoxetine	Case report	3 mo	60 mg/d	Moderate improvement in PTSD symptoms
Shay 1992[47]	28	Fluoxetine	Open series	12–27 mo	20–80 mg/d	13 of the 18 with explosiveness showed reduced explosiveness and anger; 22 had improvement in depression; no comment on symptoms of PTSD
Davidson et al 1991[48]	5	Fluoxetine	Case series	8–32 wk	20–80 mg/d	Marked improvement in intrusive and avoidant symptoms in all 5 patients
Marmar et al 1996[49]	10	Fluvoxamine	Open trial	10 wk	110–250 mg/d	Significant improvement in intrusion, avoidance and arousal symptoms of PTSD at 4 to 6 wk
De Boer et al 1992[50]	24	Fluvoxamine	Open trial	12 wk	Up to 300 mg/d	Significant improvement for 12 subjects for PTSD symptoms; overall group quantitative improvement was modest at 12 wk
March 1992[46]	1	Fluvoxamine	Case report	NA*	250 mg/d	Reduction in both PTSD and depressive symptoms
Kline et al 1993[51]	19	Sertraline	Open trial	3 mo	50–150 mg/d	63% were positive responders on measures of PTSD, depression and anxiety
Brady et al 1995[52]	9	Sertraline	Open trial	12 wk	50–200 mg/d	PTSD and comorbid alcohol dependence; significant decrease in all 3 symptom clusters of PTSD and increase in days abstinent
Rothbaum et al 1996[53]	7	Sertraline	Open trial	12 wk	50–150 mg/d	4 of 5 completers were significant responders; average reduction of 53% in ratings of PTSD symptoms
Chen 1991[54]	7	Clomipramine	Open trial	10.57± 2.7 d	100–150 mg/d	6 of 7 patients with PTSD and OCD showed marked improvement in obsession and intrusion rating scores
Duffy and Malloy 1994[55]	13	Buspirone	Open trial	4 wk	5–30 mg/d	7 of 8 completers had a significant reduction in PTSD and depressive symptoms
LaPorta and Ware 1992[56]	2	Buspirone	Case reports	1 mo	10 mg tid	Marked or total reduction of anxiety, recollections, nightmares and insomnia
Wells et al 1991[57]	3	Buspirone	Case reports	8 mo– 1 yr	35–60 mg/d	Improved anxiety, insomnia, flashbacks, nightmares and depression

*NA = not available.

of these drugs on depression and anxiety also benefit patients with PTSD. Although patients with PTSD may begin to respond to pharmacologic treatment in the first 4 to 6 weeks, there appears to be a trend for greater global improvement in studies with a treatment duration of 8 weeks or longer,[8] suggesting that treatment trials in PTSD may need to be longer than the standard 4 to 6 weeks used for antidepressant clinical trials.

Future directions for research

Given these initial findings, the overlap of PTSD with other disorders and behaviours in which a serotonin dysfunction is present, and the paucity of research examining central serotonin function in patients with PTSD, further studies delineating the serotonergic alterations in PTSD are needed. Many of the techniques used to study the serotonin system in other disorders could be implemented. These include measuring CSF 5-HIAA and plasma or platelet serotonin levels as well as examination of serotonin receptors in postmortem brain samples.

In addition, neuroendocrine challenge is an established and minimally invasive method to study central neurotransmitter function. This method involves the use of a neurochemically specific challenge agent to stimulate a neuroendocrine response of the hypothalamic–pituitary axis. Hormone level changes induced by the challenge agent give an indirect measure of hypothalamic neurotransmitter receptor function. Indirect and direct serotonin agonists, as well as specific serotonin receptor agonists, are available for this procedure. In addition to a single neuroendocrine challenge targeting 1 neurotransmitter system, sequential neuroendocrine challenges could be administered in the same patient. For example, pairing a yohimbine challenge (a probe of adrenergic function) with a fenfluramine challenge (a serotonergic releasing agent) could define the interaction of norepinephrine and serotonin in the patient with PTSD.

Alternatively, methods of neuroimaging would enhance our understanding of the neurobiology and the involvement of serotonin in the pathophysiology of PTSD. An example is imaging of brain metabolic function to identify central nervous system regions involved in the response to the serotonin neuroendocrine challenge in patients with PTSD.

Clinical research could include the long-term study of differences in the serotonin function, symptom profile and response to treatment by type of stressor and by sex in patients with PTSD. Combat-induced PTSD and PTSD occurring in civilian life may involve different pathophysiology and show different rates of response to SSRIs. In addition, investigations of the overlap of PTSD with depressive, anxiety and personality disorders are needed, from both a psychologic and neurobiologic perspective. The nature of aggression in response to catastrophic stress and how aggression relates to subsequent PTSD should also be closely examined.

Finally, more controlled treatment trials with serotonergic medications are indicated and hold promise. Treatments with medications that have combined adrenergic and serotonergic properties should also be tested.

Conclusions

New directions in the research on the pathophysiology and treatment of PTSD will certainly include the serotonin system, given the degree of overlap of PTSD with other syndromes associated with a serotonin dysregulation and the results of SSRI treatment trials to date. Greater understanding of the neurochemical pathophysiology of PTSD and larger controlled trials may lead to improved and more efficacious treatment for PTSD.

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Minority Research Training in Psychiatry

Through a five-year, $2.5 million grant from the National Institute of Mental Health, the American Psychiatric Association (APA) is seeking through the Program for Minority Research Training in Psychiatry (PMRTP) to increase the number of minority psychiatrists entering the field of psychiatric research.

The program provides medical students and psychiatric residents with funding for stipends, travel expenses, and tuition for an elective or summer experience in a research environment, with special attention paid to trainees' career development in research. In addition, stipends are available for a limited number of one- or two-year post-residency fellowships for minority psychiatrists.

Training takes place at research-oriented departments of psychiatry in major US medical schools and other appropriate sites throughout the country. An individual at the site (the research "mentor") is responsible for overseeing the research training experience.

Administered by the APA's Office of Research, the program includes outreach efforts to identify minority medical students and residents who are potential researchers and to put them in touch with advisors who counsel them about careers in psychiatric research. Additional activities assist fellows and alumni in their research career development.

The director of the PMRTP is Harold Alan Pincus, MD; the project manager is Ernesto Guerra. An advisory committee of senior researchers and minority psychiatrists developed guidelines for applicants and criteria for selection. The members of this committee evaluate and select trainees, oversee the research training experiences, and play a role in evaluating the effectiveness of the program.

December 1 is the deadline for applications for residents seeking a year or more of training and for post-residency fellows. For medical students and other residents, applications are due three months before training is to begin. Summer medical students who will start their training by June 30 should submit their applications by April 1.

For more information about the PMRTP, call the toll-free number for the PMRTP, 800 852-1390, or 202 682-6225, or write to Dr. Pincus at the American Psychiatric Association, 1400 K St. NW, Washington DC 20005.