Clinical Case Series: The Use of Desvenlafaxine and Duloxetine for Combat Related Post Traumatic Stress Disorder among Operation Iraq Freedom and Operation Enduring Freedom Combat Veterans

Including a Supplemental Appendix Introducing a Novel Psychotropic Drug Combination Therapy We Will Call "NATIONAL CAPITAL COCKTAIL (NCC)

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Abstract

Background: Post-traumatic stress disorder (PTSD) is an anxiety disorder that can arise after exposure to a terrifying event/ordeal in which there is severe physical harm or threat thereof. Symptoms include persistent re-experience of the trauma, avoidance of trauma-associated stimuli, and hyperarousal. The clinical course is driven by pathophysiologic changes and heightened responsivity in the amygdala and hippocampus, hypofunction of the medial prefrontal cortex, hyperfunction of the sympathoadrenal axis and a reduced activity of the hypothalamic-pituitary-adrenal axis. Objective: There is both serotonergic and noradrenergic dysregulation in patients with PTSD. Venlafaxine extended release (VER), a Serotonin (5-HT) Norepinephrine (NE) reuptake inhibitor (SNRI), was found in two randomized trials to be more effective in reducing PTSD symptoms than placebo. As such, SNRI's are listed as first line therapy for post-traumatic stress disorder (PTSD) by both Department of Defense (DOD)/Veterans Affairs (VA) treatment guidelines and leading psychopharmacology textbooks. A case report anecdotally reported a reduction of PTSD symptoms with the SNRI desvenlafaxine (DSV). On the basis of these reports that SNRI's reduce sympathetic arousal and are effective in treating the hyperarousal, reexperiencing, and impulsivity seen in PTSD, we've evaluated two other SNRI's duloxetine (DLX) and DSV effects on combat related PTSD.Method: Nine military service members on an inpatient psychiatric unit reported distressing combat PTSD symptoms, were diagnosed with PTSD, and were prescribed either DLX or DSV as part of their medication regimen.Results: Eight service members experienced a significant reduction of symptoms in all three PTSD domains. Both agents were well tolerated. Conclusion: SNRI's as a class of medication for PTSD appears highly beneficial for symptoms associated with combat PTSD. These findings provide a rationale for a placebo-controlled trial to establish efficacy of DLX and DSV for PTSD.

Introduction

In addition to Selective Serotonin Reuptake Inhibitors (SSRI's), SNRI's are also considered first-line psychopharmacotherapy by both the Department of Defense/Veteran's Affairs clinical practice guidelines for

PTSD[1] and well respected psychopharmacology textbooks[2]. These guidelines are based on limited trials utilizing VER only[3,6]. Venlafaxine is supported as efficacious in PTSD treatment[3,6]. While SNRI's as a class of medication are indicated for PTSD, the evidence supporting the two other agents (DSV & DLX) in the SNRI class is extremely limited. Anecdotally, both DSV and DLX have been used quite often in the author's clinical practice with efficacy. However, a review of current literature on the use of the specific SNRI's DSV and DLX for PTSD, yielded three case reports[7,9], one observational naturalistic study[10], one trial[11], four trials currently in progress[12,15], and one pilot study[16].

The Diagnostics of PTSD

Post-traumatic stress disorder (PTSD) is an anxiety disorder that can arise after exposure to a terrifying event/ordeal in which there is severe physical harm or a threat of physical harm (trauma)[17]. PTSD is classified as an anxiety disorder due to the preponderance of anxiety based symptoms[17]. The first diagnostic criteria of PTSD is the trauma, which includes exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways; (a) Directly experiencing the traumatic event or events, (b) Witnessing, in person, the event or events as it occurred to others, (c) Learning that the traumatic event or events occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event or events must have been violent or accidental, (d) Experiencing repeated or extreme exposure to aversive details of the traumatic event or events (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse). Criteria does not apply to exposure through electronic media, television, movies, or pictures, unless their exposure is work related[17]. Appendix A, Diagnostic Criteria of Posttraumatic Stress Disorder 309.81 (F43.10).[17] Other PTSD symptoms include persistent re-experience of the trauma, avoidance of trauma-associated stimuli, and hyperarousal[17,18]. After trauma in which the victim experiences actual or threatened death or serious injury, four dimensions of PTSD symptoms unfold[17]; (a) Intrusive re-experiencing the event with distressing recollections, dreams, flashbacks, and/or psychologic and physical distress, (b) persistent avoidance of stimuli that might invite memories or experiences of the trauma, (c) Negative alterations in cognitions and mood, and (d) increased arousal and reactivity[1]. PTSD and anxiety in general have many of the symptoms and signs of fear[18]. PTSD, however, lingers long after the stress stimulus has lifted and the threat has passed. Just as chronic pain is a type of pain that no longer serves a useful purpose, chronic anxiety/fear as seen in PTSD also serves no useful purpose[18]. Intrusive re-experiencing is characterized by the presence of one (or more) of the following intrusion symptoms associated with the traumatic event or events, beginning after the traumatic event or events occurred[17]; (a) Recurrent, involuntary, and intrusive distressing memories of the traumatic event or events, (b) Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event or events, (c) Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event or events were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.), (d) Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event or events, or (e) Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event or events. Avoidance is characterized by[17]; persistent avoidance of stimuli associated with the traumatic event or events, beginning after the traumatic event or events occurred, as evidenced by one or both of the following; (a) Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event events, or (b) Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event or events.[17] Negative alterations in cognitions and mood associated

with the traumatic event or events, beginning or worsening after the traumatic event or events occurred, as evidenced by two (or more) of the following[17]; (a) Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined"), (b) Persistent, distorted cognitions about the cause or consequences of the traumatic event or events that lead the individual to blame himself/herself or others, (c) Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame), (d) Markedly diminished interest or participation in significant activities, (d) Feelings of detachment or estrangement from others, or (e) Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).[17] Hyperarousal is characterized by marked alterations in arousal and reactivity associated with the traumatic event or events, beginning or worsening after the traumatic event or events occurred, as evidenced by two (or more) of the following[17]; (a) Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects, (b) Reckless or self-destructive behavior, (c) Hypervigilance, (d) Exaggerated startle response, (e) Problems with concentration, or (f) Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

Clinical Course and Pathophysiology of PTSD

With a lifetime prevalence of 8% in the general population and up to 19% among service members/veterans who have experienced combat from Vietnam and Operations Enduring Freedom and Iraqi Freedom (OEF/OIF) wars, the clinical course is driven by pathophysiological changes affecting the neurobiology of NE and 5-HT.[10,18-23]. Pathophysiologic changes include heightened responsivity in the amygdala and hippocampus, hypofunction of the medial prefrontal cortex, hyperfunction of the sympathoadrenal axis and a reduced activity of the hypothalamic-pituitary-adrenal axis with both serotonergic and noradrenergic dysregulation[10,18-23].

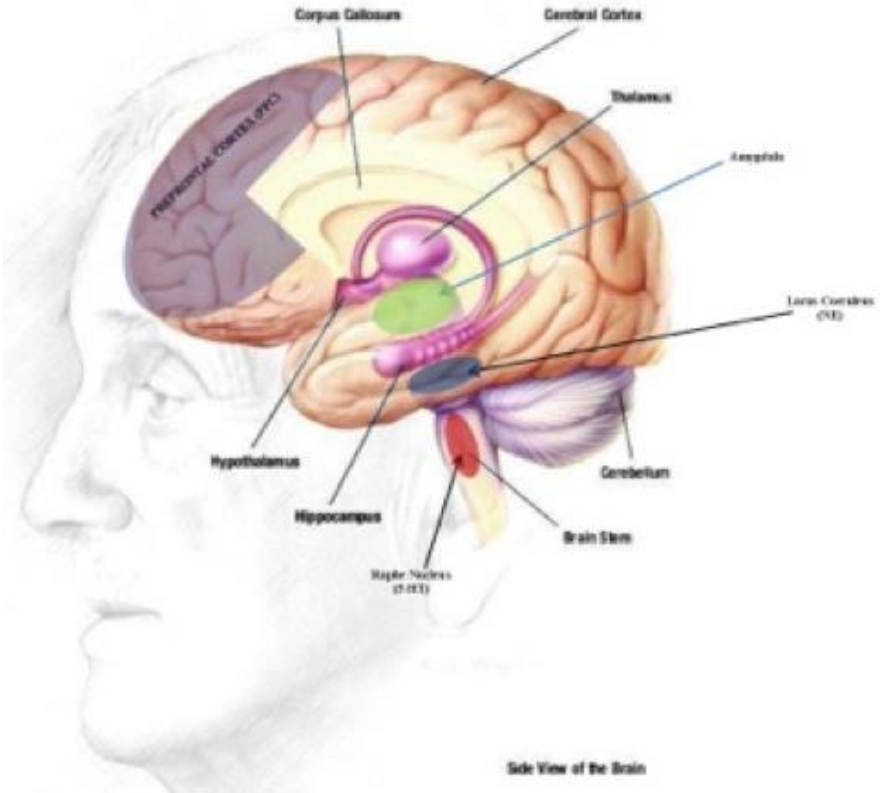
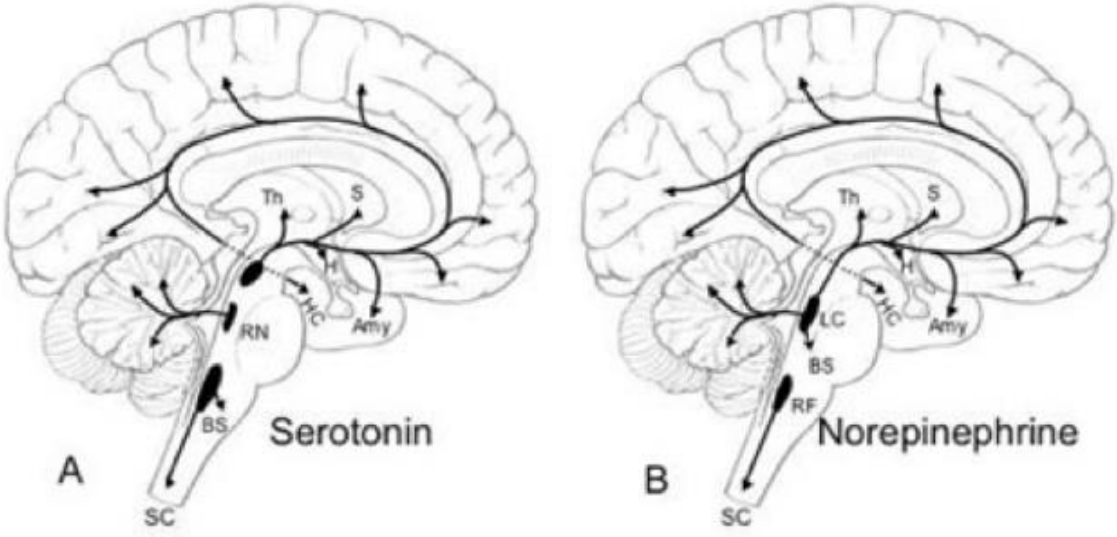


Image 1: Relevant Brain structures in PTSD (a public domain JPG image):

The precise mechanisms underlying the pathogenesis of PTSD remains unclear, but evidence supports decreased serotonergic function, and both 5-HT and NE dysregulation[24]. Lower levels of 5-HT, reduced serotonin transporter (SERT) binding, lower levels of NE and reduced norepinephrine transporter (NERT) binding is associated with PTSD symptoms[24]. At the center of the central nervous system involved in the fear response is the amygdala which governs our ability to experience fear[18]. There is subsequently a balance between emotion, attention, and cognitive processing through higher cortical structures (PFC). Processing through the PFC, which controls executive function, serves in part to balance the fear response and thalamus and amygdala hperactivity. With dysregulation of 5-HT and NE in PTSD, the ability of normal PFC function to aid in balancing the thalamus and amygdala hperactivity is diminished. Subsequently increased "emotional valence" brings about a more heightened sense of danger to global situations[18]. Current hypothesis on the role of NE in PTSD also includes (but not limited to) modulation of activity in areas of the brain involved in anxiety, namely the amygdala and locus coeruleus[24]. NE dysregulation includes also depending on the area of the brain either hypo or hyper levels of NE with associated dysregulation in NERT [7,24]. It is suggested that an oversensitive noradrenergic system underlies some of the symptomology of PTSD such as heightened startle response, hypervigiliance, and increased arousal[7,24].

Image 2: Diagram of 5-HT and NE pathways in the brain (a public domain JPG image):



The following is a summary of dysregulation among 5-HT, NE, and the brain areas and pathways has been found associated with PTSD symptomology (note – a full review of the neurobiology and pathophysiology is beyond the scope of their report):

a. Increased and spontaneous firing of NE neurons within and from the locus coeruleus[24].
b. Dysregulation of 5-HT neuron firing within and from the rahpe nucleus [24].
c. Increased SERT in the cortex, increasing reuptake of 5-HT, therefore decreasing 5-HT levels in cortex areas associated with anxiety[24].
d. Increased NERT in the cortex, increasing reuptake of NE, therefore decreasing NE levels in cortex areas associated with anxiety[24].
e. Heightened responsivity in amygdala (low 5-HT, high NE) [14,26].
f. Heightened responsivity hippocampus (low 5-HT, high NE)[14,26].

g. Hypofunction of the medial prefrontal cortex (low 5-HT, low NE)[18].Hyperfunction of the sympathoadrenal axis (high NE)[18].
h. Reduced activity of the hypothalamic-pituitary-adrenal axis (through negative feedback secondary to the stress response to NE and increased cortisol)[14,25-28].
i. Increased emotional valence (reduced ability of PFC to balance emotional response[18].
j. Deregulated and mismanaged hippocampus memories and PFC cognitive processing of the stimulus or traumatic experience (hyperactive hippocampus and hypoactive PFC)[14,25-28].

In an effort to further aid the target audience on the pathophysiology and neurobiology of PTSD, the authors drew image 3. Their image represents a balance scale where PFC function on one side works with and counterbalances the thalamus and amygdala on the other side. With normal functioning, homeostasis stays with in normal limits and normal daily fluctuations, and the individual is free of symptoms, has optimal level of functioning, and is free of anxiety symptoms (other than the daily normal ups and downs). PTSD symptoms are likely to emerge when either (a) the thalamus and amygdala are in hyperfunction (with normal or mildly low PFC function), or (b) the PFC is in hypofunction (with either normal to mild hyperfunction of the thalamus and amygdala), or (c) both thalamus and amygdala are hyperfunctioning, and PFC is hypofunctioning. The operators within the brain structures with hyper and hypo functioning of brain structures are the neurotransmitters 5-HT and NE. The hippocampus influences the PFC functioning, however, the amygdala influences the hippocampus especially during the early stages or initiation of PTSD symptoms, thus decreasing the ability of PFC to regulate and balance homeostasis.

Image 3: Pictorial diagram of Normal Brain Functioning

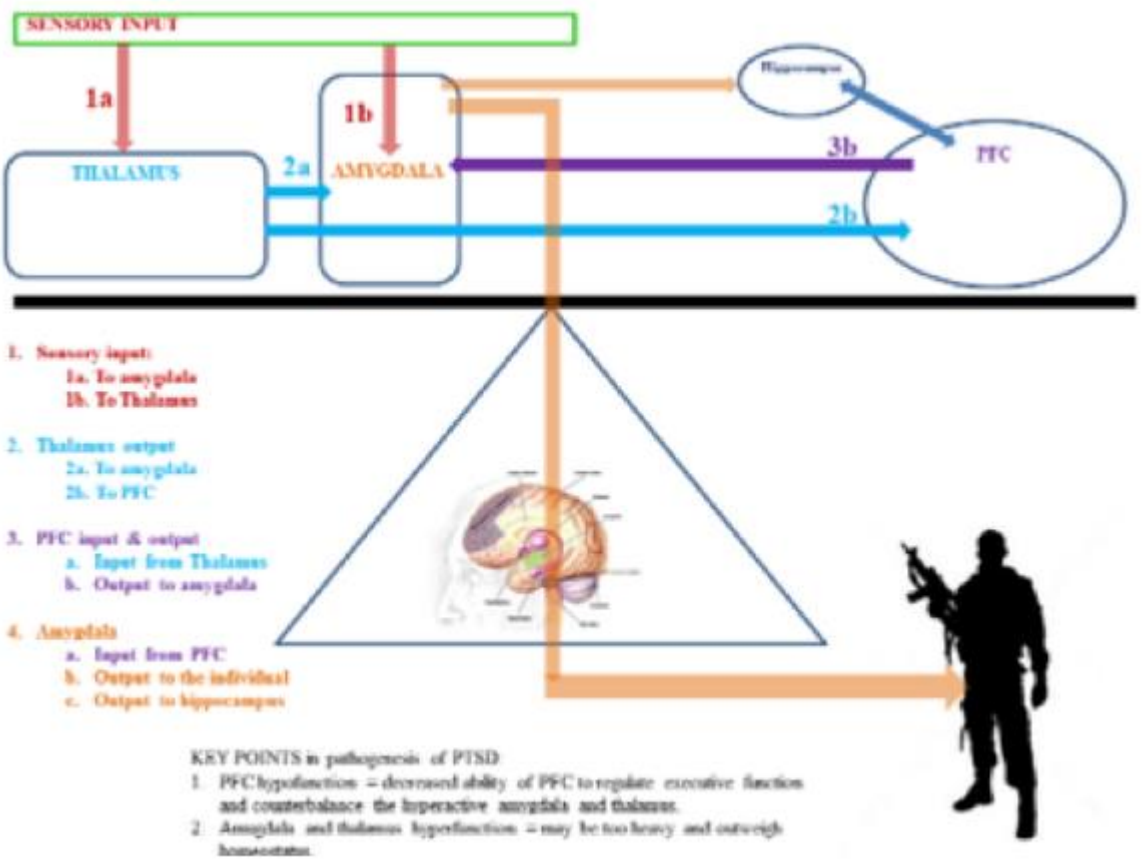
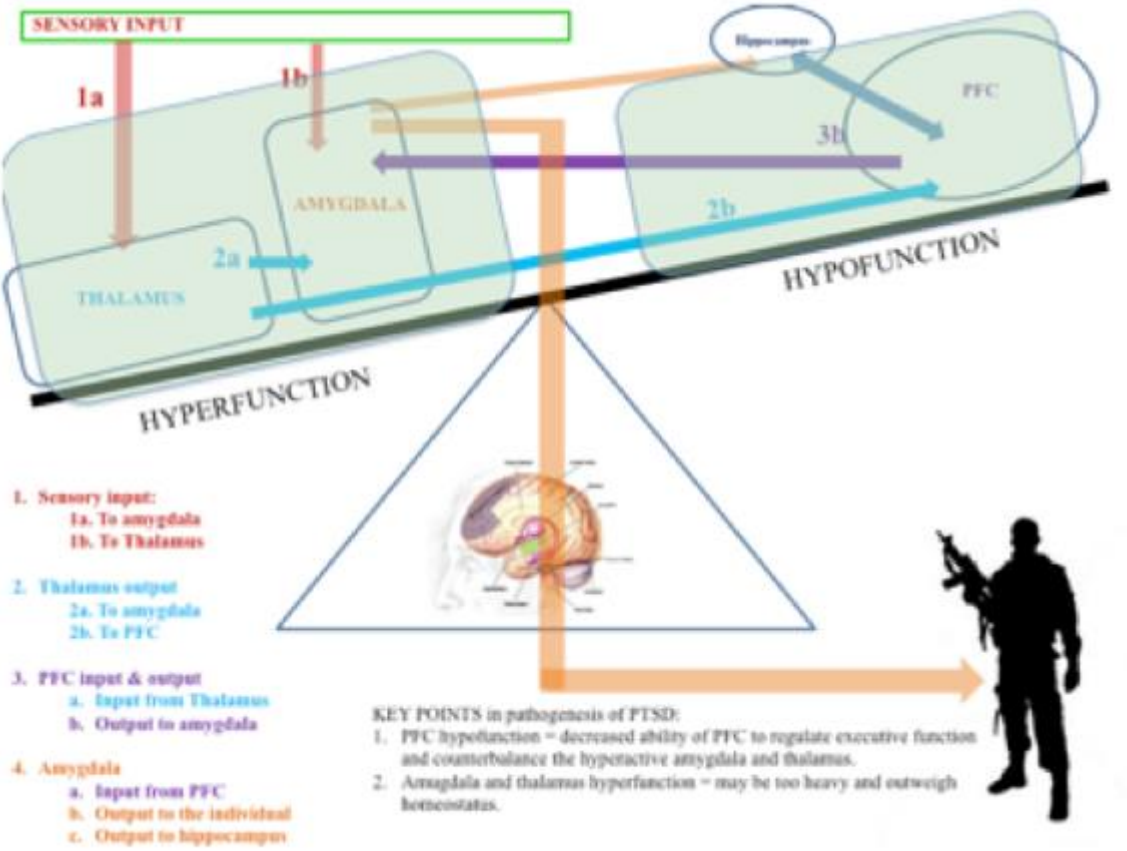


Image 4: Pictorial diagram representing brain function and PTSD symptoms (a) Thalamus & Amygdala Hyperfunction (outweighing) PFC function, (b) PFC hypofunction not able to counterbalance thalamus and amygdala function.



PTSD Treatment

PTSD treatment includes; (a) immediate management and relief of distressing signs and symptoms, (b) management of trauma-related comorbid conditions, (c) non-pharmacological interventions including cognitive behavioral treatment, and (d) psychopharmacologic agents including antidepressants, antianxiety medications, mood stabilizing drugs, and antipsychotics[14]. The goals of treatment are management of symptoms and optimization of level of functioning[1,24]. The gold standard for PTSD is psychotherapy in combination with psychotropic medication[1,29]. The recommended first line treatment recommended is an SSRI or SNRI to target anxiety symptoms[1,2]. The aim of PTSD treatment is to reduce re-experiencing of the traumatic event, avoidance, numbing, and hyper-arousal. Treatment should relieve distress and improve functioning and quality of life. As described above, the 5-HT and NE systems, brain structures, and neuropathways are implicated in the etiology of PTSD. A variety of processes have been proposed as described above for both 5-HT and NE dysfunction in PTSD including; (a) deficient or excessive innervation to key structures and cellular mechanisms, (b) abnormal regulation of 5-HT and NE release, reuptake, or abnormal responsiveness to 5-HT/NE signals: all which may lead to abnormal neurotransmission. The SERT and NERT transporter sites are the primary targets of the SNRI's increasing the respective neurotransmitters in their respective pathways bringing about regulation and balance. The result is regulation of both 5-HT and NE in the appropriate pathways and brain structures as indicated above in images 1-4 to bring about

homeostasis pictured in image 3 above. Modulation of both serotonergic and noradrenergic systems has proven to be a successful approach in the pharmacologic treatment of PTSD.[10,18,24,29]

Method

Walter Reed National Military Medical Center (WRNMMC), Bethesda Maryland inpatient psychiatry department has encountered a substantial number of returning combat veterans from both Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) (combat in Afghanistan), presenting with recurrent, distressing, combat related PTSD symptoms. Reports estimate that 20-30% of Iraq and Afghanistan War Veterans have symptoms of a mental disorder including PTSD[26]. PTSD and traumatic brain injury are considered the "signature injuries" of the Iraq and Afghanistan Wars. PTSD and traumatic brain injury are considered the "signature injuries" of the Iraq and Afghanistan Wars[27]. WRNMMC providers have been prescribing DSV and DLX in addition to VER for diagnosed combat PTSD with symptoms in all three symptom domains. Clinical justification for prescribing DSV and DLX for PTSD include that SNRI' are (a) considered first-line psychotropic therapy, (b) anecdotal reports that all three SNRI agents (DSV, VER, DLX) have been used and have markedly reduced combat trauma related symptoms in OIF and OEF combat veterans, and (c) proven efficacy of VER with chemical similarity of VER to DSV and DLX. Their report describes encouraging responses to DSV and DLX among these service members. It became apparent to prescribing providers that (a) results were being seen with DSV and DLX, and (b) there was a paucity of evidence with no randomized control trial directly supporting efficacy of DSV and DLX.

Results

We modeled their clinical case series after similar case series for combat related PTSD in a military hospital [32]. In addition to the primary author being the primary inpatient psychiatric provider with prescribing privileges for the cases indicated in their report, when it was apparent that a set of important data was emerging on the use of DSV and DLX for combat PTSD, a retrospective review of records was conducted. The retrospective record review was completed with PTSD severity of symptoms and treatment response to the various agents rated in similar fashion with the same rating scales used in the aforementioned case report [32]. All cases were considered successful and responsive in that they were admitted to an acute inpatient psychiatric unit, treated, stabilized, and discharged with a reduction of symptoms. In addition to achieving acute stability, all cases were retrospectively scored using the Clinical Global Impression of Change, which used a 7-point scale that ranges from markedly improved to markedly worse[32-34].

Results

Of the 10 patients prescribed the SNRI's either DSV or DLX, 6 were prescribed DLX and 4 were prescribed DSV. To provide a global rating of illness severity, improvement and response to treatment, all 10 cases were rated on the Clinical Global Impression of Change Scale[32-34]. While on the acute inpatient psychiatric unit with lengths of stay between 3-5 weeks, 5 patients were rated as marked improvement, 4 were rated as moderate improvement, and 1 was rated minimal improvement. The 4 with moderate improvement were with more severe PTSD symptoms and once acutely stabilized were transferred to PTSD specialty care. Upon review of outpatient records after PTSD specialty care, all 4 initial moderate responders continued on a positive response trajectory eventually able to be rated with marked response. The 1 patient rated with a

minimal response was not vested in their treatment and care, and will not be discussed further. Both DLX and DSV were essentially equally efficacious (in percentages) in patients rated with marked response with 2 for DLX and 3 for DSV respectively. Both agents were essentially equal with more severe symptoms rated as moderate response during the initial rating period, however all continued with symptom reduction and positive continued response with a longer rating period. While all 9 patients were eventually rated with a marked response, those with more severe symptoms took longer. By the end of 9 weeks, all 9 patients were rated with marked response.

Table 1: Initial Rating Period (3-5 weeks): Treatment Response of patients on an acute inpatient psychiatric unit.

(level of response)	**Minimal**	**Moderate**	**Marked**
(number in category)	1	3	6
Categories without regard to combination therapy versus monotherapy			
Duloxetine	1	3	2
Desvenlafaxine		1	3
		(4)	(5)
Broken Down with Regards to Monotherapy versus Combination Therapy		**Moderate**	**Marked**
Duloxetine + Mirtazapine		2	1
Desvenlafaxine + Mirtazapine		1	2
Duloxetine		1	1
Desvenlafaxine			1
		(4)	(5)

Table 2: Extended Rating Period (6-9 weeks): Treatment Response of the 4 with combined acute inpatient psychiatric stabilization and specialty PTSD care.

	Moderate	Marked
Duloxetine + Mirtazapine		2
Desvenlafaxine + Mirtazapine		1
Duloxetine		1
Desvenlafaxine		
		(3)

The following is a summary of observations and questions that arouse

1. By the end of 9 weeks, whether on dual psychopharmacotherapy of monotherapy, all 9 patients were rated with marked response.
2. The more severe the PTSD symptoms, the longer the response time.
3. Total of 9 patients. 6 were on Dual agent therapy with one agent being either DSV or DLX combined with Mirtazapine (MTZP), and 3 were on monotherapy or either agent.
4. Of the dual therapy patients, 50% were rated marked, and 50 % rated moderate. Thus, it is likely the severity of symptoms and not the particular SNRI agent that determined the level of response per given time.
5. Of the Dual Therapy patients, 3 were DSV/ Mirtazapine (MTZP) and 3 were DLX/MTZP. 66% of those on DSV and MTZP responded markedly in the 3-5 week period while 33% responded moderately. Whereas with DLX/MTZP, 33% responded markedly and 66% moderately in the 3-5 week period. Their might raise the question as to if DSV/MTZP dual therapy if more efficacious or with faster action than DLX/MTZP.
6. Of the monotherapy patients, 100% of patients on DSV responded markedly compared to those on DLX where 50% responded markedly and 50% responded moderately.
7. The small numbers of patients is a limiting factor.
8. Whether dual or monotherapy, DSV has more percentage responding markedly within the 3-5 week period. By 9 weeks all were with marked response. Question: Does DSV yield a faster response?

Representative Cases

Four representative cases are presented to illustrate the types of combat trauma encountered, the major presenting symptoms and the responses to either DSV or DLX. Two cases highlight response to DSV and two cases highlight response to DLX.

DSV

Case 1 MDD & PTSD
(DSV 50 mg and MTZP 15 MG)

A 28 year-old active duty US Marine with one combat deployment to Iraq in 2004 – 2005 with combat in Fallujah during some of the heaviest most violent combat in the war. 10 years time in service (TIS). In addition to the constant danger and high level of alertness their Marine had 2 instances of direct trauma to where they experienced traumatic brain injury with loss of consciousness and altered mental status. In November 2004, their vehicle was hit with and improvised explosive device (IED). In December 2004, their guard tower was hit with a mortar, and they fell 30 feet and lost consciousness for "a few minutes." In both instances, other Marines in their military unit were killed. They experienced extreme survivor's guilt. Present illness began with a progressive decline in functioning with predominant mood and anxiety symptoms since redeployment in 2005. Illness spans a seven-year period prior to current treatment with progressively more frequent and intense periods of depressive symptoms, alcohol dependence, and PTSD culminating in four suicide attempts between July 2011 and July 2012. Diagnosed with Depression and PTSD. PTSD symptoms included hypervigilance, agitation, irritability, inability to slow down, relax, and difficulty sleeping with delayed onset, frequent awakenings, intermittent nightmares, persistent triggers, avoidance by isolation and alcoholism. Symptoms were rated as moderate in accordance with diagnostic criteria[13,28-30]. Treatment efforts had included numerous trials of SSRI's with poor response. Efforts also included the SNRI Effexor with mirtazapine (dubbed California Rocket Fuel {2}), however they experienced an adverse event on Effexor and were switched to DSV with MTZP. They were followed inpatient for 5 weeks and symptoms had improved to the point where they were safe and stable for discharge, and CGI response was rated as marked. Medications were all well tolerated. Final medication regimen was DSV 50 mg and MTZP 15 MG. NOTE: Their case sparked the author's interest on using alternative SNRI agents for PTSD, and highlighted that alternative SNRI agents have their place in PTSD treatment. Subsequently, WRNMMC providers began using all SNRI agents for PTSD.

Case 2 MDD & PTSD
(DSV 50 mg and MTZP 15 MG)

Patient is a 43 year old Soldier with 10 TIS. Patient is a 3 time combat veteran. Their most traumatic deployment was to Iraq in 2005 - 2006 where they worked as a Blackhawk door gunner. Their deployment was significantly traumatic for the patient in that they experienced a number of firefights, was blown up with an improvised explosive device (IED), was shot 3 times; twice in their left leg wants in their right shoulder. Patient has shrapnel from the IED in their right shoulder. Furthermore they described having engaged in hand to hand combat and was stabbed on the left side of their forehead. Patient described during their deployment when their vehicle was blown up, the blast from the IED rendered them having altered state of consciousness where they were dazed, confused, and seeing stars. Patient received no further workup for traumatic brain injury. Patient describes symptoms consistent with posttraumatic stress disorder where hypervigilant is present with; difficulty sleeping, irritability, difficulty concentrating, not wanting to be around crowds, isolating, somewhat increased startle response, and having difficulty being in a room out

their back to the wall facing the door. They described consistent symptoms of avoidance to where they isolate, avoids people, places, and things that trigger memories. They described re-experiencing with dreams often, and nightmares with some consisting of "dead folks are mad at me," to where people that died in their proximity and that they killed while deployed were in their dream. Patient described certain smells and sounds remind him of difficult experiences in Iraq. They further described feeling anxiety and triggered with people of Arabic descent, consistent with the enemy he was fighting while deployed. Final medication regimen: DSV 50 mg and MTZP 15 MGDLX

Case 3. MDD & PTSD
(DLX 60 mg, MTZP 15 MG, and Seroquel XR 100 mg po qhs)

33 year old US Marine. Patient was admitted from the emergency room after meeting with their outpatient provider, and disclosing frustration and suicidal ideation in the context of unresolved and untreated chronic physical pain in their knees and shoulder, and unresolved untreated continued anxiety and PTSD symptoms more specifically disturbing nightmares. Patient described their suicidal ideation in terms of merely thinking of suicide as an option to experience relief from their pain and nightmares. Nonetheless, their expression of suicide as an option to relieve their pain and nightmares was concerning enough to be admitted on the acute inpatient unit. He was deployed in 2005 - 2006, and experienced a blast injury when their vehicle was hit with an IED, and he was knocked unconscious. During their incident of being knocked unconscious, in the vehicle, the vehicle was crushed, and the weapon of the vehicle, a 50 caliber machine gun, twisted and ended up pointing at him right in their chest with a live round inside. They described being unconscious for a period of time and then waking up, to find themself at the end of a live round. The entire experience is very disturbing to the patient. Furthermore the patient described an incident where they had to shoot a woman who was deemed a threat and came near their vehicle. They describe continuing to relive images of the woman, in addition to the nightmares surrounding the incident of having a 50 caliber machine gun appointed at their chest. They continued to have these dreams almost nightly, and reports the prazosin and current medications ineffective. Patient describes most disturbing currently is their unrelieved chronic pain. Their pain is mostly in their right knee to where it is an “8” (1-10) chronically, with little relief. Reports he initially injured both their right and left knee from the explosion, and has had multiple surgeries. Also reports injured right shoulder during their explosion, and reinjured it 2 weeks ago. Patient endorses poor sleep roughly 3 hours a night with lots of tossing and turning. Endorses poor appetite and reports feeling "terrible." Reports memory loss and difficulty concentrating and focusing. Endorses difficulty being in crowds. Endorses desire and tendency to isolate. Reports continued nightmares. Reports continued events that trigger anxiety. Reports difficulty coping with feelings, and a tendency to try to avoid their feelings. Reports little efficacy with their current medication regimen. Final medication regimen: DLX 60 mg, MTZP 15 MG, and Seroquel XR 100 mg po qhs.

Case 4. MDD PTSD Alcohol dependence
(DLX 60 mg daily and Deplin (L-METHYLFOLATE) 15 mgs daily.

Patient is an E5/PO2 in the U.S. Navy as a corpsman with 10 years’ time in service, one combat deployment to Iraq, 1 to Kuwait, and other humanitarian and non-combat deployments with the U.S. Navy. Their combat deployment to Iraq was in 2007 with a US Marine Corps infantry unit. Their unit was a quick reaction force, as well as dismounting patrols in Aramadi, Iraq, notorious for extremely heavy fighting and violence. They were involved in a number of fire fights. Their vehicle was hit with an IED, and they were kicked in the face, but did not lose consciousness. They described having to take the life of 2 enemy combatants while deployed, and having had to provide medical care to much trauma. They describe initially upon return from

Iraq they had intrusive memories about one specific incident where an enemy was shooting at them and when they engaged this individual, the enemy went into a taxi, the patient's vehicle shot up the taxi with a 50 caliber weapon, however there was a family inside the taxi including a little girl. When the fighting ceased, the mother gave the little girl to the patient as he is a medic, however the little girl had been mortally wounded from the 50 caliber gun (her torso had been severed midline from machine gun fire, and he could not save her. The enemy in this incident had also been wounded. A US service member, as a medical professional per American medical and military doctrine, has ethical obligation to provide medical care to enemy combatants. This enemy was hurt and the patient was supposed to render care, however they did not, as they were in shock. In a dissociative state, they ended up beating the enemy to death in hand to hand combat. Subsequently they have not been able to find relief from these series of incidents. When he redeployed back to the US, they increased drinking, and became very aggressive, emotional and crying, and avoiding public places. They meet full diagnostic criteria for PTSD, with nightmares, and frequent recurring nightmares where their unit was involved in a fire fight, friendly soldiers were injured, and they could not find their medical supplies, could not help them, and they died. During humanitarian deployment to Philippines, they witnessed many dead and dismembered bodies. Final medication regimen: DLX 60 mg daily and Deplin (L-METHYLFOLATE) 15 mgs daily.

Discussion

Biologically driven by the interphase between the amygdala, thalamus, cortex, hippocampus, and other brain structures in conjunction with respective neurotransmitters, PTSD whether acute or chronic is seen quite often in Military and Veteran's Affairs inpatient psychiatric units. Patients present in various severities, at various points after the traumas, and with various combinations of symptoms among all PTSD symptom domains. A high percentage of US Military personnel exposed to combat in OIF/OEF experience distressing PTSD symptoms. Often they seek treatment immediately, however, more often they attempt to wait out or avoid their symptoms in hopes of spontaneous resolution. SSRI treatment has been the common gold standard in conjunction with psychotherapy. VER/MTZP combination therapy emerged as efficacious, and also now considered first line treatment. Subsequently the Gold Standard first line PTSD treatment is SSRI or SNRI combined with psychotherapy. In the treatment of PTSD at WRNMMC, we observed that (a) DSV as monotherapy was well tolerated with positive treatment response, (b) DSV/MTZP combination therapy was well tolerated with positive treatment response, (c) DLX was well tolerated, with positive treatment response, and (d) DLX/MTZP combination therapy was well tolerated with positive treatment response. Both DSV and DLX as montherapy or in combination with MTZP, were anecdotally and naturalistically observed, and rated with a positive response on our inpatient psychiatric unit. SNRI/MTZP combination therapy (VER/MTZP) has proven tolerability and efficacy for utilization in PTSD (and treatment resistant depression) [1-6,35]. We observed a response in 9 out of 10 cases with prescribed SNRI's other than VER, positive enough to bring all patients to the point from unstable PTSD symptoms needing acute inpatient psychiatric stabilization to stable reduced symptoms able to discharge safely back into the military community. DSV, DLX, and both agents in combination with MTZP were well tolerated with no adverse events reported or observed. The response and tolerability observed here is consistent with current literature[8,9,35]. The results are promising, but must be considered preliminary.

DLX is a dual monoamine reuptake inhibitor affecting both 5-HT and NE receptors with equal affinity[2,7,36]. Our observations wit DLX were consistent with evidence[10] to where the onset of action and reduction of symptoms was more rapid and improvement was progressive and sustained. DLX has demonstrated a

relatively evenly balanced and potent inhibition of both the 5HT and NE reuptake at the transport sites and a weak effect on dopamine reuptake[24]. Duloxetine lacks affinity for muscarinic, histamine H1, alpha-1-adrenergic, dopamine D2, 5HT1A, 5HT1B, 5HT1D, 5HT2A, 5HT2C, GABA, glutamate and opioid receptors and does not exert its action through the inhibition of monoamine oxidase (MAO)[24]. Duloxetine is rapidly absorbed following oral administration, and is metabolized primarily by cytochrome P-450 (CYP) isoenzymes 2D6 and 1A2[2,24] It has been suggested that, due to a more balanced inhibition of 5-HT and NE reuptake, duloxetine can provide enhanced benefits in relieving both depression and anxiety and therefore PTSD[2,24]. DVS is the major active metabolite of venlafaxine[37]. Data indicates that DVS causes minimal inhibition of the hepatic cytochrome P450 CYP2D6 isoenzyme[37] and is listed as a minor substrate of the hepatic cytochrome P450 CYP3A4[2] indicating a lower risk of drug-drug interaction and lower risk of hepatotoxicity. Comparatively, venlafaxine is a major substrate of both hepatic cytochrome P450 CYP3A4 and CYP2D6[2]. MTZP has a unique mechanism of action via presynaptic NE alpha 2 antagonism, in essence blocking the feedback loop that would normally shut off the 5-HT and NE release into the synapse[2,36]. MTZP acts through the 5-HT and NE systems.

The authors initially did not start the PTSD treatment referenced in this report for the purposes of observation or study, but merely serendipitously discovered an important set of data emerging considered too important not to capture as a low level of evidence to support further scientific study and efficacious PTSD treatment. We therefore highlight the limitations of our case report that though the primary author was involved in the treatment of all cases referenced in this report, the data was captured and rated retrospectively. It would have been more informative to have used multiple valid, and reliable rating scales to quantify PTSD symptoms and quality of life. Unfortunately these intensive assessments were not feasible or possible retrospectively. More objective symptom ratings and responses should be included in future placebo-controlled trials. We experienced the same dilemma as in a prior similar PTSD trial[33] to where limiting our assessments using the CGI likely caused information to be missed, but did at least provide some sort of standardization of treatment response assessment. Lastly, our sample was not randomized, but rather convenient due to inpatient psychiatric admission.

Conclusion

Combat related trauma and subsequent development of PTSD is commonplace among military service members of all branches of the US Military. Conclusions from these anecdotal observations must be considered preliminary, however, these findings provide rationale for a placebo-controlled trials to establish scientific efficacy in this population. PTSD among the military and veteran population will persist for years. Where PTSD is considered by some[18] to be related in part to a “recovery failure from a universal set of emotions and reactions” to severe stress, it is well recognized as treatable with reduction and elimination of symptoms possible and improved quality of life attainable for sufferers. It is encouraging that trials are currently underway exploring both DLX and DSV as additional treatment strategies for PTSD. The acquisition of PTSD and conditioned fear responses depends, in part, on the functioning of noradrenergic and serotonergic neurotransmitter systems[16]. Noradrenergic function, hyperfunction, and dysregulation, is positively associated with the acquisition of PTSD symptoms[16]. Similarly, hypofunction or inhibition of serotonergic function is positively associated with the acquisition of PTSD symptoms[16]. As such, all SNRI’s (not solely VER), with their broader mechanism of action targeting both 5-HT and NE, could be utilized for patients with combat PTSD. Further studies and trial are needed to be rated as efficacious for PTSD.

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Appendix A: Diagnostic Criteria of Posttraumatic Stress Disorder 309.81 (F43.10) (13)

Note: The following criteria apply to adults, adolescents, and children older than 6 years. For children 6 years and younger, see corresponding criteria below.

Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:

- Directly experiencing the traumatic event(s).
- Witnessing, in person, the event(s) as it occurred to others.
- Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
- Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse).
  - **Note:** Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.

Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:

- Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).
  - **Note:** In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.
- Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).
  - **Note:** In children, there may be frightening dreams without recognizable content.
- Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.)
  - **Note:** In children, trauma-specific reenactment may occur in play.
- Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
- Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:

- Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
- Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

- Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
- Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").
- Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
- Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
- Markedly diminished interest or participation in significant activities.
- Feelings of detachment or estrangement from others.
- Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

- Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.
- Reckless or self-destructive behavior.
- Hypervigilance.
- Exaggerated startle response.
- Problems with concentration.
- Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month.

The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The disturbance is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.

Specify whether:

With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

- **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
- **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).
- **Note:** To use this subtype, the dissociative symptoms must not be attributable to the physiological effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify if:

With delayed expression: If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate).

Posttraumatic Stress Disorder for Children 6 Years and Younger

In children 6 years and younger, exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:

- Directly experiencing the traumatic event(s).
- Witnessing, in person, the event(s) as it occurred to others, especially primary caregivers.
  - **Note:** Witnessing does not include events that are witnessed only in electronic media, television, movies, or pictures.
- Learning that the traumatic event(s) occurred to a parent or caregiving figure.

Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:

- Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).
  - **Note:** Spontaneous and intrusive memories may not necessarily appear distressing and may be expressed as play reenactment.
- Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).
  - **Note:** It may not be possible to ascertain that the frightening content is related to the traumatic event.
- Dissociative reactions (e.g., flashbacks) in which the child feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) Such trauma-specific reenactment may occur in play.
- Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
- Marked physiological reactions to reminders of the traumatic event(s).

One (or more) of the following symptoms, representing either persistent avoidance of stimuli associated with the traumatic event(s) or negative alterations in cognitions and mood associated with the traumatic event(s), must be present, beginning after the event(s) or worsening after the event(s):

- **Persistent Avoidance of Stimuli**
- Avoidance of or efforts to avoid activities, places, or physical reminders that arouse recollections of the traumatic event(s).
- Avoidance of or efforts to avoid people, conversations, or interpersonal situations that arouse recollections of the traumatic event(s).
  - **Negative Alterations in Cognitions**
- Substantially increased frequency of negative emotional states (e.g., fear, guilt, sadness, shame, confusion).
- Markedly diminished interest or participation in significant activities, including constriction of play.
- Socially withdrawn behavior.
- Persistent reduction in expression of positive emotions.

Alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

- Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects (including extreme temper tantrums).
- Hypervigilance.
- Exaggerated startle response.
- Problems with concentration.
- Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

The duration of the disturbance is more than 1 month.

The disturbance causes clinically significant distress or impairment in relationships with parents, siblings, peers, or other caregivers or with school behavior.

The disturbance is not attributable to the physiological effects of a substance (e.g., medication or alcohol) or another medical condition.

Specify whether:

With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and the individual experiences persistent or recurrent symptoms of either of the following:

- **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
- **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).
- **Note:** To use this subtype, the dissociative symptoms must not be attributable to the physiological effects of a substance (e.g., blackouts) or another medical condition (e.g., complex partial seizures).

Specify if:

With delayed expression: If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate).

Appendix B

Introducing "NATIONAL CAPITAL COCKTAIL (NCC):" A Connotation for the SNRI Agents Desvenlafaxine or Duloxetine in Combination with Mirtazapine for Treatment in Combat PTSD

(Put Forth by a Team of US Military Providers In Reverence to Dr. Steven Stahl's "California Rocket Fuel" venlafaxine/mirtazapine combination therapy)

We would like to introduce "NATIONAL CAPITAL COCKTAIL (NCC)", to connote what we have determined in the above case series as very powerful combinations of psychopharmacotherapy Desvenlafaxine/Mirtazapine and Duloxetine/Mirtazapine for service members with combat PTSD. Psychiatry practice at Walter Reed National Military Medical Center (WRNMMC) sees many men and women with combat PTSD, who often require a combination of psychotropic drugs. As referenced above in the case series, WRNMMC providers have been prescribing the alpha 2 antagonism (Mirtazapine) and SERT/NET reuptake inhibitor (Venlafaxine, Desvenlafaxine, and Mirtazapine) combinations. WRNMMC providers have been prescribing not only the Venlafaxine/Mirtazapine combination ("California Rocket Fuel"), but also "NCC," consistently, regularly, and with good response. While researching the literature on combination therapies, the author's discovered the combination for treatment resistant depression termed "California Rocket Fuel" by world renown psychiatrist, psychopharmocologist, and researcher; Dr. Steven Stahl. The term "California Rocket Fuel" is well known among the WRNMMC inpatient psychiatry staff providers as well as throughout the psychiatry community in general. We were curious as to the origins and history of the name connoting the venlafaxine/mirtazapine drug combination. This appendix is to merely reference "California Rocket Fuel" and to introduce "NATIONAL CAPITAL COCKTAIL (NCC)."

Dr. Steven Stahl's was kind enough to respond to our request for information on his use of the term "California Rocket Fuel," which is referenced throughout the literature in addition to the Gold Standard psychopharmacology (a) prescribers guide - Stahl, SM. The Prescriber's Guide: Stahl's Essential Psychopharmacology, 3rd ed. New York, NY: Cambridge University Press; 2009, and (b) textbook – Stahl, S.M. Stahl's Essential Psychopharmacology, Neuroscientific Basis and Practical Applications, 4th Edition, New York, NY: Cambridge University Press; 2013. The following excerpt is from personal communication via email with Dr. Stahl (April 16, 2014 at 12:37:05 PM EDT) obtained by author US Navy Ensign Colin M. Smith:

> "Interesting question. This came from the era of the first edition of my textbook, Essential Psychopharmacology, in 1996, when I had thought about the synergy between alpha 2 antagonism and SERT/NET reuptake inhibition and had tried the combination in my private practice empirically and found that it worked well. I was trying to think of a name that would connote powerful efficacy and be catchy, and since I am in California and this combination blasted difficult patients out of the deep pit of their depression, I thought we could imply a launch to wellness with the idea of California rocket fuel, with the meds providing the fuel to rocket a patient out of deep depression into wellness. It stuck. I have named other combinations, but some have not caught on as well, including for bipolar disorder depending upon the bias/teaching of the medical center, e.g., Boston Bipolar Brew (any combo but never an antidepressant); Buckeye bullets (from Cleveland studies of many combinations of Seroquel, also called Quel kits), California careful cocktail (antipsychotics first, then add antidepressant carefully) and Tennessee Mood Shine (From Vanderbilt) antidepressant first, then add antipsychotic. The point is to make things easy to learn, easy to remember and memorable." (stevestahl.com, Stephen M. Stahl <>)We find it appropriate and fitting in the spirit of Dr. Stahl's "California Rocket Fuel," to introduce our term "NCC,"in our treatment of combat PTSD. We expect to see more and more use of Desvenlafaxine/Mirtazapine and Duloxetine/Mirtazapine in combination therapy for combat PTSD in years to come.