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## PTSD and Current Translational Research

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### 1. Introduction

Posttraumatic stress disorder (PTSD) is a chronic and disabling anxiety disorder that occurs after a traumatic event. In this chapter, we will briefly discuss current research in concept, diagnosis and treatment strategies of PTSD. In addition, we will introduce the concept of biomarkers for PTSD. In each section, we will focus on the discussion of current translational research in PTSD, including clinical and molecular studies in PTSD. Specifically, we will discuss the strategies of translational studies, from bench to bedside and from bedside to bench, two research approaches in the development or identification of PTSD biomarker, a novel approach to diagnosis and treatment. Recent data from the national co-morbidity survey indicates PTSD prevalence rates are 5% and 10% respectively among American men and women. The prevalence of PTSD in the military population is much higher from 10% to 30%.

### 2. Concept of PTSD

PTSD is a type of anxiety disorders. Its onset may occur soon after a major trauma, or be delayed by more than 6 months after the event. When PTSD occurs, it usually gets better after 3 months. However, some people will suffer chronically from PTSD, lasting for many years. PTSD can occur at any age and can follow a natural disaster such as a flood or fire, or events such as war, a prison stay, assault, domestic abuse, and/or rape. The terrorist attacks of September 11, 2001, for example, caused PTSD in people who were involved, witnessed the disaster, or lost relatives and friends. PTSD can also occur in military service members during war, such as the Iraq war. These traumatic events can produce stress in all involved, but less than 30% of those involved develop PTSD. PTSD patients exhibit depressive symptoms, abnormality of the circulating levels of the stress hormones and neurotransmitter activity, and alteration of gene expression. PTSD symptoms have been around for long time. The significance of PTSD came to public attention only recently.

### 3. Historical changes in the concept of PTSD in diagnosis

Throughout our history, PTSD has been called a number of other different names. It was called soldier's heart for soldiers who developed the symptoms of PTSD after the Civil War and combat fatigue or shell shock for soldiers after World War I. During the World War II, it



was called battle fatigue or gross stress. PTSD was recognized as one of mental disorders by the American Psychiatric Association (APA) officially and was added to the Diagnostic Manual of Mental Disorders (DSM), in 1980s. The DSM-III diagnostic criteria for PTSD were revised in DSM-III-R (1987) and DSM-IV (1994). A very similar syndrome is classified in ICD-10.

It is the Vietnam War that brought significant public attention to this emotional disorder. In 1980, PTSD was recognized as a disorder by the American Psychiatric Association (APA) and was added to the Diagnostic Manual of Mental Disorders (DSM). In fact, before PTSD was recognized as an emotional disorder, it was considered to be nothing more than cowardice or personal weakness<sup>1</sup>.

PTSD also has one or more comorbidities. These common co-morbid diagnoses include major affective disorders (MDD), bipolar disorder, dysthymia, alcohol or substance abuse disorders, anxiety disorders and personality disorders. The mechanisms underlying the high rate of co-morbidity seen with PTSD are still unknown. There are no exclusionary criteria in DSM-III-R. Diagnostic criteria for PTSD include a history of exposure to a "traumatic event" and symptoms from each of three symptom clusters: intrusive recollections, avoidant/numbing and hyper arousal symptoms. Duration of symptoms is considered as a fifth criterion. The following are the common symptoms - a three-factor PTSD structure in the DSM system.

#### 4. Current studies of PTSD symptom models and diagnosis

Although the PTSD symptoms of three-factor (re-experience, avoidance/numb, and hyper-arousal) has been considered as the diagnostic categories in the DSM system, several studies found three factors to be insufficient<sup>2</sup> and proposed several alternative models. In 1998, King et al<sup>3</sup> proposed a model of four-factor, which comprises re-experience, avoidance, emotional numbing, and hyper-arousal by separating the Avoidance/Numbing factor into two factors: Avoidance and Emotional Numbing. Their studies are supported by other groups, which conducted the factor analysis<sup>4-6</sup>.

Simms et al<sup>7</sup> proposed another four-factor model in 2002. Their model includes re-experiencing, avoidance, dysphoria, and hyper-arousal. The difference between their model and King's model is that they separated hyper-arousal symptoms into a larger dysphoria factor as a non-specific PTSD component, representing a general level of distress<sup>6-12</sup>. It is possible that different models can be used for analyzing different data sets<sup>6</sup>. For example, the model proposed by Simms et al<sup>7</sup> may be useful for analysis of the PTSD Checklist (PCL) data<sup>13</sup>, while the model proposed by King et al<sup>3</sup> may analyze the Clinician Administered PTSD Scale<sup>14</sup>. Currently, it is still a challenge to determine the symptom structure of PTSD in the DMS system.

The current PTSD criteria miss several reactions that many trauma survivors experience. There is a new study suggesting that the current diagnostic procedures for PTSD are insufficient<sup>15</sup>. The study believes that some items need to be added in the current criteria including the nature of a traumatic event to reflect the relevancy of an individual's subjective experience in determining what constitutes a traumatic event<sup>15</sup> and claims that both objective and subjective factors are relevant. They report that individuals adapt to extreme experiences in a highly complex and coordinated manner. Trauma response is multifaceted and includes appraisals and thoughts, emotions and behaviors. However, it is difficult to quantify an experience whether it is traumatic objectively. Individual variation is



induced by many factors. Thus, trauma or not trauma is an individual matter, interaction between the individual and his or her environment, and all parts of an individual's response. Since PTSD is a traumatic event associated disease, understanding how to define a traumatic experience is critical. It is suggested to add more appropriate criteria to more accurately categorize traumatic events. Knowing exactly what trauma is can help us to better understand who is a trauma survivor and who is not. Therefore, it is critical to keep this in our mind for the purposes of understanding the disorder and resilience, which has been shown in those who are survivors of trauma.

## 5. Research of quantification of PTSD symptoms

The PTSD diagnostic criteria have been revised several times in the DSM system. The current diagnostic criterion for PTSD is the DSM system<sup>16</sup>. In the DSM-IV-TR (2000), the diagnostic criteria (A-F) are specified below. Diagnostic criteria of DSM-IV-TR for PTSD include a history of exposure to a traumatic event, meeting two criteria and symptoms from each of three symptom clusters: intrusive recollections, avoidant/numbing symptoms, and hyper-arousal symptoms. A fifth criterion is duration of symptoms and a sixth assesses functioning.

### 5.1 The DSM-IV-TR<sup>16</sup>

#### Criterion A: stressor

The person has been exposed to a traumatic event in which both of the following have been present:

1. The person has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others.
2. The person's response involved intense fear, helplessness, or horror. Note: in children, it may be expressed instead by disorganized or agitated behavior.

#### Criterion B: intrusive recollection

The traumatic event is persistently re-experienced in at least one of the following ways:

1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. Note: in young children, repetitive play may occur in which themes or aspects of the trauma are expressed.
2. Recurrent distressing dreams of the event. Note: in children, there may be frightening dreams without recognizable content.
3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when intoxicated). Note: in children, trauma-specific reenactment may occur.
4. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
5. Physiologic reactivity upon exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

#### Criterion C: avoidance/numbing

Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by at least three of the following:



1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma
2. Efforts to avoid activities, places, or people that arouse recollections of the trauma
3. Inability to recall an important aspect of the trauma
4. Markedly diminished interest or participation in significant activities
5. Feeling of detachment or estrangement from others
6. Restricted range of affect (e.g., unable to have loving feelings)
7. Sense of foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span).

**Criterion D: hyper-arousal**

Persistent symptoms of increasing arousal (not present before the trauma), indicated by at least two of the following:

1. Difficulty falling or staying asleep
2. Irritability or outbursts of anger
3. Difficulty concentrating
4. Hyper-vigilance
5. Exaggerated startle response

**Criterion E: duration**

Duration of the disturbance (symptoms in B, C, and D) is more than one month.

**Criterion F: functional significance**

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

**Specify if:**

**Acute:** if duration of symptoms is less than three months

**Chronic:** if duration of symptoms is three months or more

**Specify if:**

**With or without delay onset:** Onset of symptoms at least six months after the stressor

In the DSM system, the "A" stressor criterion specifies that a person has been exposed to a catastrophic event involving actual or threatened death or injury, or a threat to the physical integrity. Subjects experience intense fear, helplessness, or horror, during the traumatic exposure. In the "E" stressor criterion, it is duration, which qualifies for the (chronic or delayed) PTSD diagnosis. For example, in DSM-III, the mandatory duration is six months. In DSM-III-R, the duration is one month, where it has remained in DSM-IV. Finally, the functional significance criterion (F) indicates that the subject must have significant social, occupational, or other distress as a result of these symptoms.

Since 1980, the first time the diagnosis of PTSD appeared in the DSM system, many diagnostic tools have been developed. For example, working with Vietnam War zone veterans, both psychometric and psychophysiology assessing techniques were developed. In addition, modified assessment instruments have been used in many research subjects, such as the natural disaster victims, rape/incest survivors, subjects of Sept. 11 and the military personnel who deployed to Iraq and Afghanistan wars.

Several methods have been used in quantification and assessing of PTSD symptoms, including the Clinician-Administered PTSD Scale (CAPS)<sup>14</sup> and the PTSD Checklist (PCL)<sup>13</sup>. The CAPS is a structured interview for assessing PTSD (PTSD diagnostic status and symptom severity. In the last 20 years, since it was developed at the National Center for PTSD, the CAPS has become a commonly used criterion to determine PTSD and its



symptom severity. More than 200 studies used it, indicating its excellent reliability, yielding consistent scores across items, raters, and testing occasions. It also has excellent convergent and discriminate validity, diagnostic utility, and sensitivity to clinical change. The CAPS has been used in many pharmacological treatment studies of PTSD, and modified as CAPS-2. Using CAPS-2 to examine the therapeutic response, Nagy et al<sup>17</sup> and van der Kolk et al<sup>18</sup> report that fluoxetine significantly decreased CAPS-2 total score. Katz et al<sup>19</sup> and Baker et al<sup>20</sup> also use the CAPS to examine patients' response to brofaromine. Hertzberg et al<sup>21</sup> and Busuttil et al<sup>22</sup> used the CAPS to examine inpatient group therapy. However, there are several concerns about the CAPS. First, it may take longer on paper than other PTSD interviews. Second, it may be complicated and not easy to learn. Finally, its frequency and intensity ratings overlap. The CAPS has been revised several times with the most significant revision occurring after the publication of the DSM-IV in 1994. It is suggested that CAPS diagnostic ability would be enhanced by incorporation of a multimodal assessment. Currently, in general, CAPS has been used as a screening instrument and as a self-report measure of degree of post-traumatic stress symptoms<sup>23</sup>.

Several other self-report inventories, such as Foa<sup>24</sup> and Davidson's Self-Rating PTSD Scale<sup>25</sup> and the older Impact of Events Scale<sup>26</sup> also have been used in PTSD research. Among them, Impact of Events Scale - Revised (IES-R) has been commonly used in research. IES-R is a 22-item self-report measure to assess subjective distress caused by traumatic events<sup>26</sup>. It contains seven additional items related to the hyper-arousal symptoms of PTSD. Its items correspond to 14 of the 17 DSM-IV symptoms of PTSD. It is to identify a specific stressful life event and then indicate how much the patient was distressed or bothered during the past seven days. Each of items is rated on a five-point scale ranging from 0 ("not at all") to 4 ("extremely"). The total score (ranging from 0 to 88) and subscale scores can also be calculated for the intrusion, avoidance, and hyper-arousal subscales. It is suggested to use means instead of raw sums for each of these subscales scores to allow comparison with scores from the Symptom Checklist 90 - Revised (SCL-90-R)<sup>27</sup>. While the IES-R is not used to diagnosis PTSD, it is reported that its cutoff scores can be applied in a preliminary diagnosis of PTSD.

## 6. Brain imaging and magnetoencephalography (MEG) in PTSD research

Brain image, such as functional magnetic resonance imaging (fMRI), has enhanced our ability to examine the structural and functional properties of the brain in PTSD. Several lines of evidences demonstrate that fMRI and magnetoencephalography (MEG) can be used for PTSD diagnosis and monitoring therapeutic responses. In an fMRI study, Yin et al report that PTSD patients show decreased amplitude of low-frequency fluctuation (ALFF) values in right lingual gyrus, cuneus, middle occipital gyrus, insula, and cerebellum, and increased ALFF values in right medial and middle frontal gyri, relative to traumatized individuals without PTSD<sup>28</sup>. The ALFF value in the right medial frontal gyrus is positively correlated with severity of the disorder. To examine how the function of brain changes during the recovery from PTSD, PTSD patients underwent two fMRI scans, 6-9 months apart, while viewing fearful and neutral faces in preparation for a memory test (administered outside the scanner). At the second scan, 65% of patients were in remission and their current symptom levels correlated positively with memory-related fMRI activity in the amygdala and ventral-medial prefrontal cortex (vmPFC). The change in activity of hippocampus and the subgenual anterior cingulate cortex (sgACC) is associated with the



degree of symptom improvement. These data indicate that differential brain regions within the fear network play different roles in symptom manifestation and in recovery from PTSD. The amygdala and vmPFC appear to be specific brain regions having the activity to serve as a marker for current symptom severity, while the functional changes in the hippocampus and sgACC may be a marker for recovery<sup>29</sup>. Meanwhile it is also found that there is greater recruitment and coupling of emotional brain regions during the retrieval of negatively intense autobiographical memory in the PTSD group when compared to controls<sup>30</sup>. PTSD patients have less activation to the threat condition and increased activity to the safe condition in the subgenual cingulate, ventral striatum and extended amygdala, as well as in midbrain periaqueductal grey. These data indicate abnormal reactivity in these key regions for fear expression. The temporal pattern of activity decrease found in control subjects was not obtained in PTSD patients<sup>31</sup>. Imaging analyses also find decrease of activity in the amygdala and hippocampus of PTSD patients during successful encoding of trauma-related stimuli. Such decrease in left hippocampus is associated with high arousal symptoms. These results indicate reduction of hippocampal activity under conditions of high stress and arousal<sup>32</sup>. Significant improvements of PTSD are evident on fMRI scans, and corroborated by Clinical Global Impression (CGI) scores, but CAPS scores improvements are modest, indicating CGI scores and fMRI scans can be used to examine the improvement of PTSD.

Patients with child abuse-related complex PTSD show reductions in gray matter levels in right hippocampus, right dorsal ACC and the right orbitofrontal cortex (OFC) compared to controls. Meanwhile their child abuse and hyper-arousal correlated negatively with ACC volume. Impulsivity and anger correlated negatively with hippocampus volume, and OFC volume respectively. In another study, it is found that PTSD is associated with smaller mean cornu ammonis 3 (CA3)/dentate gyrus subfield volumes and total hippocampal volume, indicating that PTSD is associated CA3 implying that chronic stress suppresses neurogenesis and dendritic branching in this structure<sup>33</sup>. As in adult PTSD, children with symptoms of post-traumatic stress suffer poor function of the hippocampus, exhibiting more errors on the recall part of the test and showing less hippocampus activity than control subjects doing the same task<sup>34</sup>.

MEG, a test that measures magnetic fluctuations faster as groups of neurons fire (neither CT scans nor MRIs can measure it), has been used for PTSD diagnosis. The MEG is cutting edge, but it's not new technology. It has been used since the late 1960s. Perhaps best of all, the mapping of synchronous neural interactions (SNI) works regardless of what the person being observed is doing. Recently one study shows that PTSD patients demonstrate a unique pattern of miscommunication. The PTSD patients show impaired. A 50-ms response (M50) gating in the right hemisphere. Thinner right superior temporal gyrus (STG) cortical thickness is associated with worse right sensory gating in the PTSD subjects. The right primary sensory cortex (S1) M50 source strength and gating ratio is correlated with PTSD symptomatology. These findings indicate that the structural integrity of right hemisphere STG cortices play an important role in auditory sensory gating deficits in PTSD<sup>35</sup>. It is found that the SNI test which assesses the functional interactions among neural populations derived from MEG recordings<sup>36</sup> can successfully differentiate PTSD patients from healthy control subjects.

## 7. Complications of PTSD

Individuals with PTSD are 8–14 times more likely to have a second lifetime diagnosis of psychosis after the development of PTSD, with 50–80% of those being affective and anxiety



disorders<sup>37</sup>. PTSD is more common among depressed primary care patients than previously thought, and 62% of individuals diagnosed with PTSD have suicidal ideation<sup>38</sup>. Here we discuss several common mental disorders seen in PTSD patients, such as alcohol and drug abuse, and depression.

### **7.1 PTSD and alcohol and drug abuse**

People with PTSD are more likely than others of similar background to have alcohol use disorders both before and after being diagnosed with PTSD. For example, 25-75% and 10-33% of survivors of abusive or violent trauma, accidental illness, or disaster trauma have problematic alcohol use, respectively. 60-80% of Vietnam veterans seeking PTSD treatment have alcohol use disorders. Veterans over the age of 65 with PTSD have increased risk for attempted suicide if they experience problematic alcohol use or depression. Those survivors with alcohol problems have ongoing health problems or pain. In addition, there is gender difference in drinking. Women who go through trauma have more risk for drinking problems. 27.9% of women with a history of PTSD report problems with alcohol abuse or dependence at some point in their Lifetime. Almost twice as many men (51.9%) with a history of PTSD reported such problems. As a point of comparison, Kessler and colleagues find that, on average, 24.75% of men and 10.55% of women without PTSD have problems with alcohol or drugs at some point in their lifetime. Alcohol use and intoxication, and suddenly stopping drinking can result in some symptoms worse, including avoidance, anger, irritability and depression. Suddenly stop drinking can also result in worsening of some the symptoms. In addition to alcohol, the consistent findings demonstrate that patients with PTSD have a high risk of drug use. For example, 34.5% of men and 26.9% of woman with PTSD also have a problem with drug abuse or dependence during their lifetime.

### **7.2 PTSD and depression**

Depression is one of the most frequent comorbid conditions in individuals with PTSD. In fact, 48% of subjects with PTSD also have current or past depression. Individuals with PTSD are almost seven times as likely as individuals without PTSD to have depression. 44.5% of individuals with PTSD one month after experiencing a traumatic event have a diagnosis of depression<sup>39-42</sup>.

### **7.3 PTSD and anxiety**

Like PTSD and depression, there is a strong relationship between PTSD and anxiety disorders. Patients with PTSD are more likely to have anxiety disorders. Around 7% of patients with PTSD at some point in their life also have had a diagnosis of Panic Disorder. Patients with PTSD are four times as likely to also have a current or past diagnosis of Panic Disorder as compared to non-PTSD control. Approximately 28% of patients with PTSD have or have had a diagnosis of Social Anxiety Disorder. Patients with PTSD are three times as likely as someone without PTSD to have Social Anxiety Disorder. It has been found that 4% to 22% of patients with PTSD also have obsessive-compulsive disorder (OCD). Finally there are strong relationships between PTSD and other anxiety disorders, such as phobia. Over 30% of patients with PTSD had or have had a specific phobia. Patients with PTSD are seven times as likely as people without a history of PTSD to have also had a specific phobia.



#### 7.4 PTSD and traumatic brain injury (TBI)

Since the war in Iraq and Afghanistan, PTSD and TBI were significantly increased in the military service members. PTSD and TBI are comorbid. Patients with both PTSD and TBI exhibit a spectrum of common clinical features such as difficulty in concentrating, sleep disturbance, depression, anxiety, irritability, fatigue, suicidality, chronic pain, and alterations in arousal. PTSD and TBI disorders have overlapping neural mechanisms with changes in hippocampal, prefrontal cortical and limbic region function because of alterations in synaptogenesis, dendritic remodeling, and neurogenesis. These neural changes in PTSD and TBI may result from pathophysiological disturbances in metabolic, cytotoxic, inflammatory, and apoptotic processes, amongst other mechanisms<sup>43</sup>.

#### 7.5 PTSD and metabolic syndrome

Several lines of research suggest that stress and post-stress adaptation responses are related to long-term health outcomes. Studies of survivors of disasters, veterans and prisoners of war, and others exposed to severe trauma, suggest higher rates of physical morbidity and mortality and increased healthcare utilization related to lifetime prevalence of trauma. Accumulating evidence from epidemiological studies demonstrate that chronic PTSD associated with trauma and secondary negative health outcomes including metabolic conditions. 43% of PTSD met criteria for metabolic syndrome, indicating that PTSD is associated with risk factors for diminished health and increased morbidity, as represented by metabolic syndrome.

#### 7.6 PTSD and pain

The co-occurrence of PTSD and chronic pain symptoms have been observed clinically. For example, it is found that 10% of patients referred to a Veterans Administration pain clinic meet criteria for PTSD and that 9.5% of patients attending a multidisciplinary chronic pain center meet criteria for "post-traumatic pain syndrome"<sup>44</sup>. In the patients who are referred for the assessment of a chronic pain problem resulting from a traumatic event, the prevalence of PTSD is also high. Hospitalized burn patients have high rates of PTSD at 12 months post-injury<sup>45</sup>. 80% of PTSD patients report the presence of a chronic pain condition. In addition, PTSD re-experiencing symptoms were positively associated with pain level and pain-related disability. The co-occurrence of chronic pain and PTSD may have implications in terms of an individual's experience of both conditions. Patients with chronic pain related to trauma or PTSD experience more intense pain and affective distress<sup>46</sup>, higher levels of life interference<sup>47</sup>, and greater disability than pain patients without trauma or PTSD<sup>48, 49</sup>. The most common forms of chronic pain for survivors of trauma are pain in the pelvis, lower back, face and bladder; and in fibromyalgia; interstitial cystitis; and non-remitting Whiplash syndromes. However, the relationship between PTSD and chronic pain is not always noticed and is often overlooked<sup>50, 51</sup>. Both PTSD and chronic pain can increase the symptom severity of either condition<sup>52</sup>. Patients with chronic pain may focus their attention toward their pain while individuals with PTSD may unknowingly focus on things that remind them of the trauma. Consequently, both PTSD and chronic pain may result in patients having less time and energy to adapt their pain and fear. Furthermore, patients with PTSD often have hyper-arousal and tension, which may interfere their perception of pain. Patients with co-morbid pain and PTSD demonstrate more intense pain, more emotional distress, higher



levels of life interference, and greater disability than pain patients without PTSD. Treating these patients can also be more complex and challenging.

Currently, the mechanism for the co-occurrence of PTSD and pain is still unknown. There are several theoretical models, such as mutual maintenance model<sup>51</sup>, shared vulnerability model<sup>50</sup>, fear-avoidance model and triple vulnerability model<sup>53</sup>. However, those models needed to be tested.

### 7.7 PTSD and other diseases

The association of traumatic life events with PTSD and other health conditions is well known. For example, patients with PTSD had substantially higher (i.e., 50–150% greater) postwar rates of many major chronic diseases, including circulatory, nervous system, digestive, musculoskeletal, and respiratory diseases<sup>54</sup>. PTSD is significantly associated with an almost two-fold increase of developing nervous system, musculoskeletal disease, and signs and ill-defined conditions of disease. PTSD is significantly associated with increased odds of developing circulatory, hypertensive, and digestive system disease<sup>55</sup>. More data shows that PTSD patients have abnormally high white blood cell counts ( $>11,000/\text{mm}^3$ ) and T-cell counts ( $>2,640/\text{mm}^3$ )<sup>56</sup>.

Evidence linking exposure to traumatic stress and cardiovascular disease is compelling. 25% of PTSD veterans report physician-diagnosed circulatory diseases (vs. 13% for PTSD negative veterans). It is also reported that PTSD veterans are significantly more likely to have had abnormal electrocardiograph (ECG) results (28% vs. 14%) with a higher prevalence of myocardial infarctions and atrioventricular conduction defects<sup>57</sup>. There are positive association between chronic PTSD and myocardial infarction (MI) as well as lower plasma levels of high-density lipoprotein-cholesterol (HDL-C)<sup>54, 57, 58</sup>. In a population study involving World War II and Korean War veterans, it is found higher rates of physician-diagnosed cardiovascular disease among PTSD subjects<sup>59</sup>. Another study among Dutch resistance fighters demonstrate increased rates of cardiovascular disease risk factors among PTSD<sup>60</sup>. A large-scale civilian population study also found an increase in ischemic heart disease among adults exposed to childhood traumas<sup>61</sup>. Furthermore, adults exposed to the Chernobyl disaster have increased rates of reported heart disease<sup>62</sup>. In addition, studies during the Beirut Civil War and the Croatia War find increases in arteriographically confirmed coronary heart disease, cardiovascular disease mortality, and increases in acute myocardial infarction (AMI) associated with exposure to these conflicts<sup>63, 64</sup>. An increase in AMIs is also reported after the Hanshin-Awaki earthquake in Japan<sup>64</sup>.

Evidence indicates that exposure to environmental stressors and subsequent development of PTSD may be related to altered neuroendocrine and immune system functions, and the onset of specific immunoendocrine-related diseases. Either increases or decreases of circulating cortisol levels in PTSD patients are reported. The former indicates an acute response or up-regulated glucocorticoid system, while later suggesting a chronic or downregulated glucocorticoid system. Either direction of these changes may result in an alteration activities of immune inflammatory. Indeed, glucocorticoids influence the trafficking of circulating leukocytes and affect functions of leukocyte and immune accessory cells. Hyper-arousal is often observed during recollection of traumatic events by PTSD victims and is associated with alterations in the neuroendocrine functions. Although these processes are complex, chronicity and excessiveness of stress system activation in PTSD could be one possible pathogenesis, which is associated with weight loss, depression,



hypogonadism, immunosuppression, and other pathophysiological conditions leading to many diseases. Therefore, the research in these specific areas is demanded and emphasized to improve the quality of life of patient with PTSD<sup>65</sup>.

## 8. Treatment of PTSD

There are many therapeutic methods for treatment of PTSD, including cognitive-behavioral therapy (CBT) and medication. In clinical study, it is reported that combinations of exposure therapy and cognitive restructuring as well as CBT produces better therapeutic response, especially in the treatment of female victims of childhood or adult sexual trauma.

The first FDA approved group of compounds for PTSD are selective serotonin reuptake inhibitors (SSRIs), including sertraline (Zoloft) and paroxetine (Paxil). In addition, there is a report showing that Eye Movement Desensitization and Reprocessing (EMDR) may have better therapeutic response as well.

Dr. Friedman suggests that mildly to moderately affected PTSD patients may need group therapy (<http://www.veterans.gc.ca/eng/sub.cfm?source=mental-health/support/factsshc>). In this therapeutic approach, the PTSD patient is asked to discuss their traumatic memories, PTSD symptoms, and functional deficits. However, since PTSD is a chronic and severely debilitating psychiatric disorder, there is no better approach yet. New ideas and approaches need to be developed. The following is a brief summary of current available approaches for treatment of PTSD.

Currently, several psychotherapies have been used in clinical practice, including CBT, exposure therapy, stress inoculation training (SIT), cognitive restructuring, and EMDR. CBT has been shown to be the most effective type of therapeutic treatment. CBT helps to recognize and change inaccurate thoughts about subjects. Exposure therapy is the best technique for recovery, involving overcoming anxieties by facing them in a controlled and safe environment and relieving fears all at once (flooding) or step-by-step (desensitization) in order to overcome them. Although this may seem frightening at first, this treatment produces a quick outcome. Supportive counseling, without facing the trauma, has also been shown to be helpful, but may not be as effective as direct exposure. The SIT consists of teaching the PTSD subjects to manage their anxiety reactions to situations, memories, etc. they normally fear and avoid. For the physical manifestations of anxiety (heart rate, hyperventilation, and muscle tension). The SIT teaches controlled breathing and progressive muscle relaxation. For intrusive thoughts and worrying, The SIT teaches patients how to interrupt their thought patterns and think of positive imagery. By this way, the PTSD can control and lessen their PTSD symptoms.

The other therapy is cognitive restructuring, which helps subjects identify and challenge their erroneous beliefs and interpretations. It is based on the idea that it is not actual events that cause negative emotional reaction but the interpretation of those events, letting to the replace worry and anxiety with more positive and productive emotions.

In addition, EMDR allows the therapist to have the PTSD patients remember their trauma briefly and then engage in cognitive restructuring.

In recent years, several alternative therapies have been introduced in PTSD treatment, although its effectiveness is still need to be determined. They are included in massage, acupuncture, art and music therapy, drama therapy and exercise.



8.1 Prognosis

The best outcome, or prognosis, depends on how soon the symptoms develop after the trauma, and on how quickly the patient is diagnosed and treated.

9. Biomarker research in PTSD

The term biomarker (biological marker) was first described in 1989 as a substance used as an indicator of a biological state. It refers to a Medical Subject Heading term: “measurable and quantifiable biological parameters (e.g., specific enzyme concentration, specific hormone concentration, specific gene phenotype distribution in a population, presence of biological substances) which serve as indices for health- and physiology-related assessments, such as disease risk, psychiatric disorders, environmental exposure and its effects, disease diagnosis, metabolic processes, substance abuse, pregnancy, cell line development, epidemiologic studies, etc”. In 2001, a definition of a biomarker was described by an NIH working group as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (NIH Biomarker Definitions Working Group, 2001). In 2004, FDA announced that quantitative measures of biological effects that provide informative links between mechanism of action and clinical effectiveness are considered to be biomarkers (FDA whitepaper ‘Innovation or Stagnation’ 2004). The World Health Organization (WHO) defines the biomarker as any substance, structure or process that can be measured in the body or its products and can influence or predict the incidence or outcome of disease (WHO International Program on Chemical Safety).

Biomarker researches progressed significantly during the 1990s. Since then, the whole field of biomarker research has been drastically changed by the human genome project. The information gained from the human genome project redirected biomarker studies into a whole new era. High-throughput analytical instruments have been used to screen thousands of genes and proteins simultaneously. Today, biomarkers have been classified into four subgroups including type 0 biomarker, type 1 biomarker, surrogate end point-type (type 2 biomarker) and risk marker.

<b>Type 0 biomarker:</b> A marker of the natural history of a disease and correlates longitudinally with known clinical indices.
<b>Type I biomarker:</b> A marker that captures the effects of a therapeutic intervention in accordance with its mechanism of action.
<b>Surrogate end point (type 2 biomarker):</b> A marker that is intended to substitute for a clinical end point; a surrogate end point is expected to predict clinical benefit (or harm or lack of benefit or harm) on the basis of epidemiological, therapeutic, pathophysiological, or other scientific evidence.
<b>Risk marker.</b> For prevention, the important disease risk factors are those that can be measured quantitatively in the subject at risk. These factors can be used to identify cohorts for prevention. Those may also be used as endpoints in prevention studies.

Table 1. Identification of Biomarkers



9.1 Potential biomarker(s) for PTSD

High-throughput “omic” approaches including genomics, proteomics, and metabolomics have been used in candidate biomarker selection and identification for many diseases<sup>66</sup> (Table 2). However, progress of the search for PTSD biomarkers has been slow and often frustrating because the complexity of the molecular mechanisms of the disease and the undefined validation process. Potential biomarker(s) for PTSD on the basis of animal research<sup>67</sup> or limited studies in humans have been proposed. But confirmation and validation of their clinical utility have not been accomplished. Appropriate and efficient validation would be expedited with valid animal models, standardized laboratory practice, larger human population-based studies, and repeated sampling of individuals. A strategy used in biomarker development for other illnesses<sup>68</sup> can also be used for development of a blood biomarker test for PTSD. Here, we will discuss the strategy including screening approach as well as analytical and clinical validations to facilitate PTSD blood biomarker discovery and selection.

Technology	Method	Test
Genomics	SNP genotyping	Susceptibility or disease modifying gene
	Positional cloning/microsatellites	Fine mapping/sequencing of disease loci
	Microarray	Gene expression
Proteomics	2DGE, MS, LC-MS, GC-MS, MS-MS, MALDI-TOF MS	Protein expression
Metabolomics	NMR spectroscopy, MS, infrared spectroscopy	Small molecule

Table 2. Biological tools are used in screening PTSD biomarker

In the case of PTSD, to screen the potential biomarkers, researchers currently compare the gene and protein expression profiles or alteration of a gene, protein expression or metabolite levels between PTSD patients and healthy control subjects by using several well developed procedures (Table 1). Biomarkers may be obtained from saliva, blood, cerebral spinal cord fluid, urine and tissues. It also can be physiological parameters such as blood pressure<sup>69</sup>, ECG<sup>70</sup>, and heart beating<sup>71</sup>, transmitters, such as 5-HT<sup>72</sup>, dopamine<sup>73</sup> and GABA<sup>74</sup> or their metabolites, and brain-imaging<sup>75</sup>. Biomarkers indicate PTSD or PTSD characteristics, including the level or type response of exposure to a traumatic stress, genetic susceptibility, genetic responses to traumatic stress exposure, markers of subclinical or clinical state, or indicators of response to therapy. These markers may dynamically alter during the course of PTSD development or differentially change after single or multiple traumatic stresses, respectively (Table 3).



Potential biomarker	References
T cell phenotypes	Lemieux A, Coe CL, Carnes M. 2008 <sup>76</sup>
Assumptions	Rosen GM, Lilienfeld SO. 2008 <sup>77</sup>
Erythrocyte sedimentation rate, white blood cell count, and cortisol/dehydroepiandrosterone-sulfate ratio	Boscarino JA 2008 <sup>78</sup>
Endothelial dysfunction in plasma	von Känel R, 2008 <sup>79</sup>
Serum interleukin-2 and interleukin-8 levels	Song et al. 2007 <sup>80</sup>
Platelet serotonin concentration	Kovacic Z et al., 2008 <sup>72</sup> Pivac N, et al., 2006 <sup>81</sup> Mück-Seler D, et al., 2003 <sup>82</sup> Spivak B, et al., 1999 <sup>83</sup>
Platelet MAO-B activity	Pivac, N et al., 2007 <sup>84</sup>
Circulating Cortisol levels	Meewisse ML et al., 2007 <sup>85</sup> Ehlert U et al., 2001 <sup>86</sup> Heber R, et al., 2002 <sup>87</sup> Glover DA, Poland RE, et al., 2002 <sup>88</sup> Yehuda R, et al., 2002 <sup>89</sup>
Glucocorticoid receptor (GCR) expression in lymphocyte	Gotovac K, et al., 2003 <sup>90</sup>
WFS1 gene	Kesner Y et al, 2007 <sup>91</sup>
Baseline level of platelet-leukocyte aggregates, platelet CD63 expression, and soluble P-selectin concentration	Vidović A et al., 2007 <sup>92</sup>
GABA plasma levels	Vaiva G et al.. 2006 <sup>93</sup>
S-100B and neuron-specific enolase	Sojka P et al., 2006 <sup>94</sup>
NPY expression	Dutton MA, Lee EW, Zukowska Z. 2006 <sup>95</sup>
Myelin basic protein	Wang Q, et al., 2004 <sup>96</sup>
C-reactive protein and serum amyloid A	Söndergaard HP, et al., 2004 <sup>97</sup>
Urinary dopamine	Glover DA, et al. 2003 <sup>88</sup>
Thyroid hormone	Garrison RL, Breeding PC. 2003 <sup>98</sup>
Neopterin	Atmaca M, et al., 2003 <sup>99</sup>
Plasma and cerebrospinal fluid interleukin-6 concentrations	Barker DG, et al., 2002 <sup>100</sup> Maes M, et al., 1999 <sup>101</sup>
REM latency	Reist C, et al., 1995 <sup>102</sup> Kauffman CD et al, 1987 <sup>103</sup>
Average heart rate responses to a series of sudden, loud-tone presentations	Pitman RK, et al., 2006 <sup>104</sup> Bryant RA. Et al., 2007 <sup>105</sup>
Mixed lateral preference and parental left-handedness	Chemtob CM, Taylor KB, 2003 <sup>106</sup>
Startle responses	Milde AM, et al., 2003 <sup>107</sup>

Table 3. Potential Biomarkers for PTSD



PTSD biomarkers can be the indicators of PTSD trait (risk factor or risk marker), disease state (preclinical or clinical), or disease rate (progression). The PTSD biomarkers in all possible respects: antecedent, screening, diagnostic, staging and prognosis are listed in Table 4.

Biomarkers	Function or indicator
Antecedent	Identifying the risk of developing PTSD, changes in response to single or multiple traumatic stress events
Screening	Subclinical PTSD from well adapted subjects, physiological responding
Diagnostic	Recognizing PTSD
Staging	Categorizing PTSD severity
Prognostic	Predicting PTSD course: recurrence and response to treatment

Table 4. Types of biomarker for PTSD

PTSD biomarker(s) may prove to be a single biological parameter associated with a highly specific symptom or a multiple biological indicator (cluster) related to multiple symptoms. Individual biomarkers have been shown to be a significant predictor of PTSD occurrences. Few studies have evaluated the use of multiple biomarkers for patient risk stratification<sup>67</sup>. The assessment of multiple biomarkers<sup>67</sup> may be useful for identifying subgroups of PTSD that would benefit most from additional testing.

The desirable properties of biomarkers for PTSD vary with their different usage. For example, a screening test may be used in large populations including normal and high-risk subjects. Thus, the biomarker requires having high sensitivity, specificity, and predictive values, large likelihood ratios, and low cost. A diagnostic biomarker should be appropriate for use at any stages of the disease (acute and chronic) and have consistent detectability in patients at any stage of illness or treatment. For biomarkers to be used in monitoring PTSD progression or response to therapy, features such as sensitivity or specificity may be less important because the patient serves as his or her own control (baseline values are compared with follow-up values). The ability to monitor intra-individual variation as this relates to clinical status is more important. Costs may be less important for prognostic markers since only people with PTSD will be tested. Searching for prognostic PTSD biomarkers may be most challenging because it requires a larger sample and prospective design, whereas a diagnostic biomarker test requires relatively smaller sample size and a cross-sectional design. While all the features of biomarkers can be combined in one for a screening test, having specific features for specific use is the ultimate goal in the search for PTSD biomarkers. It would be ideal to have a biomarker that can differentiate the three conditions (physiological response, well adapted and acute PTSD) in the early traumatic stages. The overall benefit of a PTSD biomarker would be to enhance the ability of the clinician to optimally manage the patient with PTSD, and to help the researcher and clinician identify specific therapeutic targets. For instance, an EEG test may be expected to facilitate the identification of patients with sleep problems. A biomarker such as the level of glucocorticoid<sup>108</sup> and/or concentration of epinephrine in the blood may help to differentiate subjects who have transient acute response to traumatic stress from patients who ultimately



develop PTSD. A plasma GABA level may represent a marker of recovery from trauma<sup>93</sup>. In general, a biomarker test for PTSD should be not only accurate, reproducible, and standardized, but also acceptable to PTSD patients and easy-to-use for clinicians.

9.2 A strategy to identify a PTSD biomarker

Like studies of biomarkers in other medical fields, the strategy for identification of a PTSD biomarker includes three major steps: screening, analytical validation and clinical validation (Fig 1).

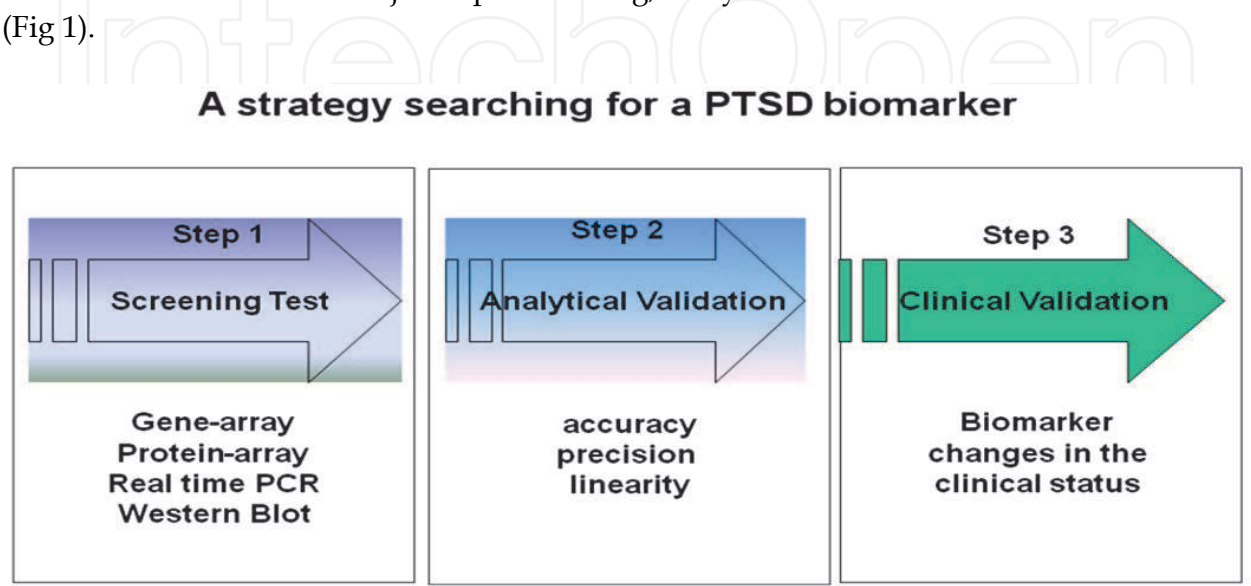


Fig. 1. A strategy searching for a PTSD biomarker

9.2.1 Screening a biomarker(s) for PTSD

Currently, many biological tools have been used for screening potential PTSD biomarkers (Table 2). Biomarker screening is the first step in identifying a potential PTSD biomarker. During the screening stage, animal models have been used. However, the complexity and variability of PTSD symptoms make the establishment of generally validated animal models for biomarker screening more challenge<sup>67</sup>. The most current animal models use different stress paradigms to provoke a wide range of behavioral responses. In addition, results have been presented as mean values (with SD or SE) of the entire exposed population. These animal models may overlook the clinical finding that only a proportion of individuals (20%–30%) who are exposed to a "traumatic event" will eventually develop PTSD<sup>67</sup>. Therefore, multi-dimensional validation, such as a combination of both behavioral and biological criteria, may be necessary to provide a solid basis for the biomarker screening study and for the molecular mechanism research<sup>67</sup>.

Compared to other psychiatric and medical illnesses relatively little work has been directed toward elucidating the molecular mechanisms of posttraumatic psychopathology. There are some association studies for individual molecular targets, but these are inherently limited to hypothesis-driven search for candidates already implicated through the current framework of biological theorizing. Previously, the possibility of identifying molecular targets for PTSD in a genome-wide screen in a validated animal model using microarray gene expression profile analysis have been discussed<sup>67</sup>. The mRNA levels of p11, a member of the S-100 protein family, increase in the post mortem prefrontal cortex (area 46) of PTSD patients<sup>109</sup>. Stress, induced by three days of inescapable shock, increases both p11 mRNA levels in the prefrontal cortex (PFC)



of rats and corticosterone levels in plasma. Dexamethasone (Dex), a synthetic glucocorticoid, up-regulates p11 expression in SH-SY5Y cells through glucocorticoid response elements (GREs) within the p11 promoter, which can be attenuated by either a glucocorticoid receptor antagonist, RU486, or mutating two of the three glucocorticoid response elements (GRE2 and GRE3) in the p11 promoter. This work demonstrates not only an example of a study of mechanisms of posttraumatic psychopathology, but also identification of a potential PTSD biomarker, p11. Also, mitochondrial gene expression profiling in post-mortem brain of patients with PTSD<sup>110</sup> serves as a source of biomarkers. The study emphasizes the possible molecular mechanisms for PTSD, the analytical validation of sample purity, large scale scanning and cluster classification. Obtaining pure samples for genomic analysis requires highly stringent criteria and should be validated along three dimensions—analogue (similarity of behavior), predictive (predictability of drug response) and biological mechanism (gene expression). Analytical validation should also be considered.

### 9.2.2 Analytical validation for a PTSD biomarker(s)

Although several candidate biomarkers for PTSD have been identified by screening approaches, few have been validated<sup>81, 93, 108, 111</sup>. Meaningful validation requires high-throughput bioinformatics and large sets of data. In addition to statistical validation and biological/functional validation, analytical validations may be more important and have to be completed prior to their use in clinical sites. In 1999, the United States Food and Drug Administration established a final guidance for the industry validation of analytical procedures and terminology<sup>112,113</sup>. This document provides guidance on characteristics for consideration during the validation of analytical procedures. This guidance represents current thinking about validation. According to this guideline, analytical validation includes the following aspects: precision (reproducibility), accuracy (clinical samples; compare to cleared or gold standard method), limit of detection, potential interferences software, sample preparation/conditions, performance around the cut-off, potential for carryover or cross-hybridization and assay limitations. Obviously, the guideline can be used for analytical validation of PTSD biomarkers. In this guideline many concepts or terms were defined. We review several major terms related to PTSD biomarker development here. First is **precision**. In the guideline, precision was defined as reproducibility, which requires that intended users using clinical samples and all analytical steps of the assay get reliable results; User training should be the same for studies and for marketed assay. Precision is considered at three major levels: repeatability, intermediate precision and reproducibility. Repeatability expresses the precision under the same operating conditions over a short interval of time and is also termed intra-assay precision. Intermediate precision expresses within laboratory variations (different days, different analysts, different equipment, etc). Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology) and is assessed by means of an inter-laboratory trial.

The second term that we discuss here is **accuracy**. The accuracy of an analytical procedure expresses the closeness of agreement between the value, which is accepted either as a conventional true value or an accepted reference value. Accuracy requires the use of real clinical samples; to compare to a reference method; in limited cases (i.e., very rare alleles) contrived samples can be used; samples should mimic the molecular composition and concentration of real clinical samples. This is sometimes termed 'trueness'.

The third term is the **detection limit**. The detection limit is determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at



which the analyte can be reliably detected. The detection limit of an analytical procedure is the lowest value of analyte in a sample. The marker can be detected but not necessarily quantitated as an exact value. Visual evaluation can be used for non-instrumental methods but may also be used with instrumental methods. Signal-to-noise with this approach can only be applied to analytical procedures which exhibit baseline noise. The signal-to-noise ratio can be determined by comparing measured signals from samples with known low concentrations of analyte with those of blank samples. A signal-to-noise ratio between 3 or 2:1 is generally considered acceptable for estimating the detection limit.

It is also noticed that in the screening stage, microarray has emerged as an important format for simultaneous analysis of tens of thousands of substances present in a sample. Successful adaptation of microarray assays to clinical diagnostics will require particular attention to issues of quality control and quality assurance. Results of an assay can be compromised by a number of pre-analytical factors including the quality of the reagents (e.g., the microarray and the detection reagents) and the integrity of the sample. Similarly, numerous factors in the analytical phase of a microarray assay may compromise results, including changes in the reaction conditions and calibration. Furthermore, a microarray study combines many reagents or samples in a single device. This process brings additional confounds not usually encountered in discrete testing of a single analysis in a single sample. Thus, various strategies, such as replicate analysis and normalization have to be implemented to control and assess analytical factors in these studies. The current range of measures taken to ensure the analytical accuracy and quality of data generated from proteomics and metabolomics assays in other fields may also be applied in the context of DNA microarrays. Taking everything together, the data have to be documented with analytical validation for each of the operator and instrument prior to clinical validation.

### 9.2.3 Clinical validation for PTSD biomarkers

As a newly discovered biomarker assay makes the transition from a research setting to the clinical diagnostic laboratory, it should progress through defined stages of assay confirmation. At the screening stage, a validation focused on evaluation of research assay technology, performance, and specifications (analytical validation) is most important. However, the ultimate goal is validation of the test ability to identify PTSD. Assays have to be developed into final procedures that are standardized and reproducible for clinical diagnostic implementation. Thus, the final step of development of PTSD biomarker should be clinical validation (clinical utility).

Clinical validation or clinical utility will be based on new clinical trial data. These clinical data should be prospectively collected in a longitudinal study with appropriate institutional review board (IRB) and informed consent. These clinical samples must be well characterized. They will show clinical utility in prospective clinical studies and retrospective validation. Clinical and analytical cut-off points should be described and independently validated. Clinical cut-off points should be identified in a training set and validated in a test set. Clinical cut-offs can reference data from literature. Bridging studies are required if a platform change or device change is necessary after clinical validation.

For markers of clinical status, clinical validation refers to measurement of how biomarker level is related to a change in the clinical status of a patient<sup>114</sup>. The changes are not compared only with the average normal, but to the patient's own baseline values obtained when they are first diagnosed with the same procedure. The dynamic changes of the biomarker value in the same patient indicate the inherent variability of the data. The variability can be due in



part to the reproducibility of the analytical measurement, but also due to natural physiological changes or PTSD progression. Therefore longitudinal study of a control (healthy) population may be needed to determine the extent to which level changes represent biological variability rather than changes in disease status. In addition, to determine the relationship of biomarker alteration between peripheral and central nervous system (CNS) could be more important in clinical validation study for PTSD. We found that biomarkers in the brain and in the blood are not necessarily altered in the same direction. Finally, the validity of the biomarker test, including its rates of false negatives and false positives should be well-established before the tests enter clinical use.

Currently, the diagnosis for PTSD is based on a certain set of symptoms determined from the patient's clinical history, mental status examination, duration of symptoms, and clinician administered symptom checklists or the patient self-report. However, there are no available laboratory biomarker tests for PTSD. To begin intervention at the earliest possible time, priority must be given to developing objective approaches to determine the presence of PTSD. Thus, a simple blood test or a biomarker that could detect PTSD in its earliest and potentially most treatable stages would be beneficial for physicians and patients. Currently, many potential biomarkers have been identified in animal models and in patients with PTSD. But those biomarkers have not been well validated. Current strategy to identify a biomarker for PTSD involves pre-clinical screening, analytical validations and clinical validations. This strategy will enhance not only the study of the molecular mechanisms of PTSD, but also the translation of basic science to clinical implications.

During the last decade, with the rise of genomics and advances in molecular biology, researchers have become increasingly focused on the underlying molecular mechanisms of PTSD and searching for a biomarker for PTSD. New technologies have the potential to identify PTSD biomarkers in blood to definitively diagnose patients with PTSD or to identify those who may be at high risk for developing PTSD after traumatic exposure. The development of such biomarker tests requires a strategy that involves pre-clinical screening, analytical validations and clinical validations, and is driven by the advances in research surrounding the underlying molecular mechanisms of PTSD (Fig 1).

The first potential PTSD biomarker has been discovered. In 2009, we reported that p11 mRNA expression is significantly changed in post mortem cortex of patients with PTSD and depression, and in their peripheral blood mononuclear cells (PBMC). We hypothesize that p11 mRNA levels in the peripheral blood cells can serve as a biomarker for PTSD with heterogeneity in terms of type of trauma, time since trauma and duration of illness. We examined the PBMC p11 mRNA of patients with PTSD ( $n = 13$ ), major depressive disorder (MDD,  $n = 16$ ), bipolar disorder (BP,  $n = 24$ ), and schizophrenia (SCZ,  $n = 12$ ) or controls ( $n = 14$ ) using quantitative real-time PCR and the circulating levels of cortisol in blood plasma and saliva of PTSD patients using radioimmunoassay kit CORT-CT2. The Hamilton Rating Scale for Depression (HAMD) and Anxiety (HARS), the Chinese version of the Davidson Trauma Scale- Frequency (CDTS-F) and the Chinese version of the Davidson Trauma Scale-Severity (CDTS-S), and Impact of Event Scale-Revised (IES-R) were administered. We found that patients with PTSD had lower levels of p11 mRNA than control subjects, while those with MDD, BP and SCZ had significantly higher p11 levels than the controls. P11 mRNA levels were positively correlated with the scores of HAMD ( $r = 0.62$ ,  $p < 0.05$ ), CDTS-F ( $r = 0.71$ ,  $p < 0.05$ ) and CDTS-S ( $r = 0.62$ ,  $p < 0.05$ ), while they did not correlate with scores of HARS and IES-R. Basal levels of plasma and salivary cortisol of PTSD patients were not



statistically different from those of controls. Our findings suggest that PBMC p11 mRNA expression levels may serve as a biomarker to distinguish PTSD from BP, MDD and SCZ.

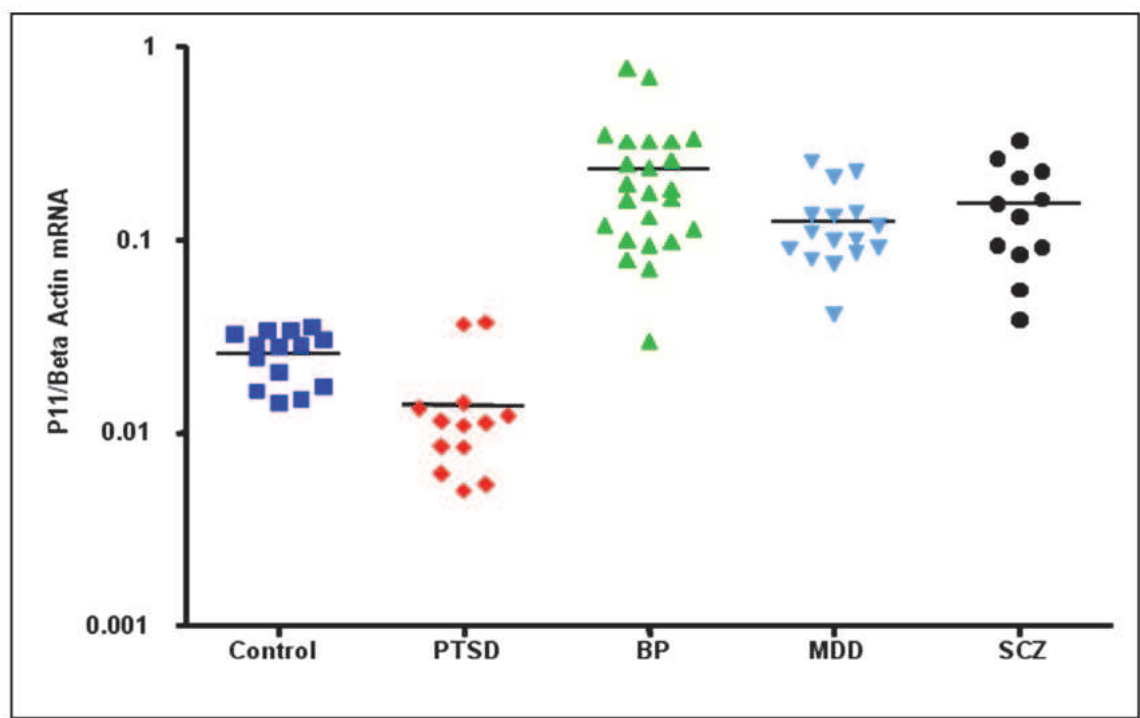


Fig. 2. Significantly lower p11 mRNA levels in the patients with PTSD compared to control and other mental disorders. BP, Bipolar, MDD, Major depressive disorder, SCZ, schizophrenia.

In the table 5, we summarized potential biomarkers in gene association studies.

Gene	Methods	Results	Reference
Serotonin transporter	Association analysis	The low-expression variant (short allele) modifies risk of PTSD.	115-119
Cytomegalovirus gene (CMV)	Methylation microarrays to assay CpG sites from more than 14,000 genes, among 23 PTSD-affected and 77 PTSD-unaffected individuals.	CMV-a typically latent herpes virus whose activity was significantly higher among those with PTSD.	120
FK506 binding protein 5 (FKBP5)	1143 European Americans (EAs) and 1284 African Americans (AAs), screened for lifetime PTSD. 4 SNPs in FKBP5, rs3800373, rs9296158, rs1360780, and rs9470080, were genotyped.	In AAs, one of the SNPs, rs9470080, moderated the risk of PTSD that was associated with childhood abuse	121



Catechol-o-methyltransferase (COMT) (Val158Met)	Association analysis in 424 survivors of the Rwandan Genocide.	Met/Met homozygotes exhibited a high risk for PTSD independently of the severity of traumatic load.	122
Dopamine beta-hydroxylase (DBH) (1021C/T)	Association analysis in combat veterans with (N = 133) or without (N = 34) chronic PTSD.	A significantly lower plasma DBH activity in combat veterans with PTSD carrying the CC genotype	123
Interleukin-2 (IL-2) Interleukin-8 (IL-8)	34 earthquake survivors with PTSD (according to DSM-IV criteria), 30 earthquake survivors with non-PTSD and 34 controls in northern China	Earthquake survivors with PTSD had significantly lower serum IL-8 levels. PTSD may be associated with a reduced level of serum IL-8, and traumatic survivors may be associated with a lower level of serum IL-2.	80
C-reactive protein	3049 adults living in the community (Germany). CRP, lipoproteins and triglycerides determined. Also examined blood pressure, body mass index (BMI), physical activity, comorbid somatic diseases, medication, daily alcohol intake, and depression.	PTSD positive participants significantly higher odds for elevated CRP values than those without PTSD (OR=2.27; 95% CI: 1.32-3.93). Even after adjusting for sex, age, other sociodemographic factors, BMI, blood pressure, lipoproteins and triglycerides, physical activity, comorbid somatic diseases, daily alcohol intake, and trauma exposure, almost two-fold higher odds for elevated CRP levels in participants with PTSD.	124
NPY	qPCR, SNP, western blot	Low cerebrospinal fluid NPY plasma concentrations	125-127
P11	Real time PCR, PTSD post-mortem brain and blood cells	P11 over-expressed in the CNS and down-regulated in the blood	109, 128

Table 5. Association studies: genotype and symptoms - endophenotype

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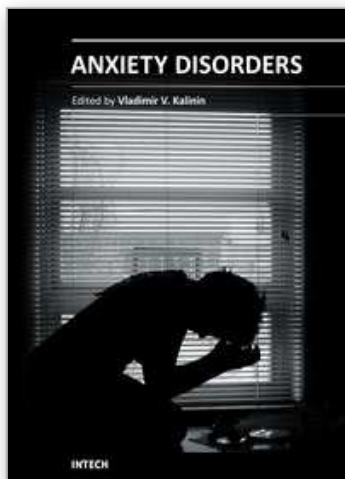


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During the last 2-3 decades drastic research progress in anxiety issues has been achieved. It concerns mostly the study of different subtypes of anxiety and their treatment. Nevertheless, the data on anxiety pathogenesis is less elaborated, although here a multidimensional approach exists. It includes neurochemistry, pathophysiology, endocrinology and psychopharmacology. Again, we are able to recognize the multifarious sense of anxiety, and the present collective monograph composed of 16 separate chapters depicting the different aspects of anxiety. Moreover, a great part of book includes chapters on neurochemistry, physiology and pharmacology of anxiety. The novel data on psychopathology and clinical signs of anxiety and its relationship with other psychopathological phenomena is also presented. The current monograph may represent an interest and be of practical use not only for clinicians but for a broad range of specialists, including biochemists, physiologists, pharmacologists and specialists in veterinary.

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