

# The role of prepulse inhibition in medication management of PTSD: A case report

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## ABSTRACT

Post traumatic stress disorder (PTSD) is defined as an anxiety disorder that can appear after exposure to a traumatic experience. This article will review a patient's history of PTSD, and course of treatment. A discussion on the available agents to properly treat this case will also be discussed.

## KEYWORDS

post traumatic stress disorder, prepulse inhibition, medication treatment

## INTRODUCTION

Post traumatic stress disorder (PTSD) is defined in the DSM-IV TR as an anxiety disorder that can appear after exposure to a traumatic experience, such as combat, and cause the individual to relive the event.<sup>1</sup> This article will review a patient's history of PTSD, his medication trials, and finally what has been found to be most effective for this particular patient case.

## CASE REPORT

A 66 year-old Caucasian male, Vietnam veteran with severe PTSD, generalized anxiety disorder, major depressive disorder and avoidant personality traits has been followed for several years at the outpatient mental health clinic for anticoagulation management. The patient has axis III diagnoses of a recent pulmonary embolism, hypertension, dyslipidemia, arthritis, and benign prostate hypertrophy. The patient was referred to mental health by primary care services due to frequent and horrific intrusive/re-experiencing PTSD symptoms. His current psychotropic medications include: prazosin 5 mg twice daily, divalproex sodium ER 2000 mg at bedtime, risperidone 2 mg at bedtime, sertraline 150 mg every morning, clonazepam 1 mg three times daily as needed, and trazodone 150 mg at bedtime.

The patient was noticeably affected by the multiple traumas he experienced in Vietnam. During the middle of

an interview regarding warfarin therapy, the patient paused and appeared distracted. Following this period, he would state his thoughts about what happened during wartime over 50 years ago. He recounted stories about holding his comrade's throat after it was slit by an enemy sword and being under fire for the next eight days with the blood remaining on his hands and clothes to remind him of the vicious killing. The veteran told tales of other horrific experiences. These experiences have left him feeling as if he cannot relate to civilians in everyday life situations, often resulting in withdrawal from group situations or having sudden outbursts of anger and aggression. The patient has a long-standing history of wartime-related nightmares, which are always disturbing and generally have a strange twist on an event which happened in Vietnam. During the daytime he is easily triggered by the sight of blood, loud sounds, and sometimes by his granddaughter, as she reminds him of a young Vietnamese girl whom he killed. The patient's fear of blood led him to thinking of cutting the top off his warfarin tablets, thereby decreasing his dose because he did not want to bleed. Outside of medical and psychological interventions provided from mental health services, the patient has been able to find peace with his wife, two dogs, and a garden which allows him to "plant flowers in the soil to cleanse his hands of the feeling of blood that is with him almost every day".

The most distant medication records available state the patient has taken paroxetine 30 mg and divalproex sodium 500 mg twice daily in 2002. The patient reported this regimen had been partially helpful in helping him sleep, but not fully. Paroxetine was increased to 60 mg daily until replaced by sertraline in 2004. Divalproex sodium dose was escalated over the years to the current dose. The patient reports that divalproex sodium has been very helpful with decreasing aggression and anger. Risperidone 0.5 mg has been taken at bedtime since 2003, and then was titrated to 2 mg, which is the current dose. There is no notation of the effectiveness of risperidone found in the notes. Clonazepam was increased from 1 mg twice daily to the current dose beginning in 2007; the patient reports this medication has been very helpful for panic attacks and sleep. Prazosin 7 mg nightly was substituted for terazosin in early 2011 in order to treat urinary incontinence and nightmares. Months later, the prazosin was increased to 5 mg twice daily to better treat incontinence. The risk of hypotension was reduced by splitting the dose to twice daily. The patient reported that the prazosin was very helpful for decreasing sweats, frequency and intensity of nightmares, and prostate problems.

## DISCUSSION

Patients may experience flashbacks or nightmares, which can cause them to relive the initial trauma.<sup>2</sup> Nightmares are memories of the experience that can be distressing to the individual.<sup>1,2</sup> This is proposed to be due to sensorimotor gating, or the method by which an individual screens the surrounding stimuli in order to filter out extraneous information and focus on what is deemed most relevant. Prepulse inhibition (PPI), or the use of a weak prestimulus to attenuate subsequent response, exists as a measure for assessing changes in sensorimotor gating and is known to be impaired in schizophrenia.<sup>3</sup> An example of prepulse inhibition is the startle response, and an exaggerated startle reflex is a marker for the diagnosis of PTSD.<sup>3</sup> However, studies of individuals with PTSD have found mixed results in terms of PPI. One study comparing a veteran population with and without PTSD found a decreased startle threshold but no difference in startle magnitude.<sup>3</sup> A meta-analysis of six studies in a population diagnosed with PTSD examined P50 auditory sensory gating, another marker for pulse inhibition.<sup>4</sup> In healthy controls, the P50 auditory potential to a second stimulus was suppressed relative to the first. Of the six studies analyzed, five reported impairments in P50 suppression.<sup>4</sup> A separate study examined PPI, P50 gating, and startle reactivity within a cohort population consisting of

individuals with and without PTSD. While those with PTSD were found to have impaired P50 suppression and increased startle response, PPI did not differ from the control population.<sup>5</sup>

PPI is regulated by the neurotransmitter, norepinephrine.<sup>6</sup> Excess stimulation of norepinephrine at alpha<sub>1</sub> receptors has been found to reduce PPI. Conversely, alpha<sub>1</sub> antagonists reverse this disruption. In particular, the effect is noted in central but not peripheral alpha<sub>1</sub> receptors.<sup>7</sup> Prazosin is a centrally acting alpha<sub>1</sub> blocker utilized in the treatment of nightmares and other symptoms of PTSD. A study by Raskind and colleagues looked at prazosin for the reduction of PTSD nightmares in the veteran population.<sup>8</sup> Most of the trials with prazosin use for nightmares were conducted in male patients; however, it is imperative to note that the incidence of PTSD is higher in the female population.<sup>2</sup> As such, it is unknown if prazosin would be as effective in women. Prazosin has been extensively studied in patients with combat related PTSD, such as our patient. It is unknown the effect prazosin would have on other subsets of PTSD.<sup>2</sup>

Though atypical antipsychotics are not approved for PTSD, they may exert a beneficial effect through actions on specific neurotransmitters. Dopamine agonists are known to reduce PPI. This reduction can be reversed by the administration of a potent D<sub>2</sub> antagonist, such as haloperidol.<sup>3</sup> The neurotransmitter serotonin also functions in regulation of PPI through action on certain serotonin receptors, including 5HT<sub>2</sub>.<sup>6, 9</sup> Stimulation of these receptors alters pre-pulse inhibition, while 5HT<sub>2</sub> antagonism may restore proper functioning. Atypical antipsychotics have affinity for both alpha<sub>1</sub> and 5HT<sub>2</sub> receptors, with relative affinity differing between agents.<sup>10</sup>

A recent study compared prazosin to quetiapine for use in the symptoms of nighttime PTSD symptoms.<sup>11</sup> The outcomes were similar between the groups regarding effectiveness. The patients who received prazosin were more likely to continue their therapy after the end of the study compared to the quetiapine treated patients. The results of the study were able to show that prazosin should be used first line in treating veteran patients with nighttime symptoms of PTSD.<sup>11</sup> In a review by Ahearn et al. examining the use of atypical antipsychotics in PTSD, they noted that risperidone, olanzapine, and quetiapine all have level B evidence for the use in PTSD, showing at least one double-blind trial with positive results.<sup>12</sup> The authors note that there are very limited data existing in the literature about side effect monitoring and long-term

outcomes in regards to the use of these medications for the treatment of PTSD.<sup>12</sup>

A recent article in the Journal of American Medical Association evaluated the use of risperidone in patients with SSRI treatment resistant, combat related PTSD.<sup>13</sup> The authors found the use of risperidone produced statistically significant reductions in the symptoms of re-experiencing ( $p=0.005$ ) and hyperarousal ( $p=0.005$ ), though not to the extent deemed minimally important by the authors. The authors concluded that the addition of risperidone to an SSRI regimen conferred no additional benefit over placebo in reducing overall PTSD severity, but could not rule out the likelihood of benefit in some patients. Additionally, the study failed to show a statistically significant change on the Clinician-Administered PTSD Scale likely due to inadequate sample size. Further long-term studies are still needed to show effectiveness and adverse effects.

SSRIs have been found to be useful in some patient populations and are prescribed more frequently in veterans for the treatment of PTSD than antipsychotics.<sup>14</sup> However, our patient was found to be SSRI-resistant, a phenomenon which is not uncommon in combat veterans.<sup>15-17</sup> The aforementioned sensorimotor gating concept may serve to explain a lack of response to SSRIs. As a class, antidepressants have not been shown to produce any changes in PPI and thus may not be appropriate for monotherapy in a veteran population where increased startle reflex is likely present.<sup>3</sup> A study examined the use of adjunct olanzapine in patients with combat related PTSD found to be SSRI-resistant.<sup>18</sup> The study was able to show the addition of olanzapine to existing SSRI therapy was beneficial in improving depressive and sleep symptoms.<sup>18</sup> Nevertheless, when global clinical improvement was assessed, results were shown to be not significantly better than placebo.<sup>18</sup> However, the small quality of life gains through the use of combination therapy with SSRIs may be valuable in difficult to treat combat related PTSD patients.

While prazosin has been determined to be an appropriate option for the treatment of some PTSD symptoms, there are less data regarding the use of antipsychotic agents. From a pharmacodynamic perspective, atypical antipsychotics represent another useful tool in the prescriber's armamentarium for treating PTSD due to their potential role in increasing PPI. More studies are warranted, especially in evaluating risk of metabolic side effects over a longer period of time. Though there is no cure for the highly debilitating condition of PTSD, our patient has had an increase in quality of life due to off-

label combination therapy. The treatment of PTSD should be symptom specific and tailored to each individual patient. Though combination therapies may not benefit all patients, these treatments may provide important quality life improvements in some patients.

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