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A Review of Interventions for Treatment-Resistant Posttraumatic Stress Disorder

Cara Katz¹, Murray Stein², J. Don Richardson³,
Soraya Seedat⁴ and Jitender Sareen¹

¹*University of Manitoba;*

²*University of California San Diego;*

³*University of Western Ontario;*

⁴*University Stellenbosch*

^{1,3}*Canada*

²*United States*

⁴*South Africa*

1. Introduction

A traumatic experience evokes a stress response and increased anxiety in those who witness or experience the event. In most, the stress symptoms will alleviate with time. However, within a significant proportion of individuals, the effects of the trauma will not diminish. Rather, residual symptoms will remain and will surface as Posttraumatic Stress Disorder (PTSD). PTSD is an anxiety disorder that can develop after one experiences or witnesses a traumatic event involving actual or threatened death or harm, or when one learns of someone else's threat of actual harm (APA Diagnostic and Statistical manual, 1994).

According to DSM-IV, PTSD manifests itself through clusters of three symptoms: re-experiencing; avoiding and numbing; and hyper-arousal. Re-experiencing the traumatic event includes recurring nightmares; flashbacks; intrusive memories or images; extreme emotional or physical responses and dissociation. The symptoms of re-experiencing the trauma can be enhanced by olfactory, visual or auditory sensory information that act as a reminder to the event. Avoidance and numbing symptoms are expressed through efforts to avoid thoughts, feelings, activities or memories associated with the trauma; alienating oneself; loss of interest in and avoidance of activities; and the inability to have loving feelings. The hyper-arousal cluster of symptoms includes increased startle responses; insomnia, in addition to other sleep issues; difficulties in concentrating; and outbursts of anger (Pivac & Kozaric-Kovacic, 2006). A positive diagnosis for PTSD includes the presence of these symptoms for at least one month accompanied with functional impairment, often including occupational and social difficulties (Bandelow et al., 2008). When symptoms last more than three months, PTSD is considered chronic (Berger et al., 2009). PTSD is often comorbid with substance abuse, major depression, other anxiety disorders and suicidality. In more severe cases, often seen in veteran populations, psychotic features and increased resistance to treatment is evident (Pivac & Kozaric-Kovacic, 2006). The present chapter will focus on the literature on the interventions for Treatment Resistant PTSD (TR-PTSD).

2. Standard first line of treatment

The goal of treating PTSD is to reduce symptom severity and frequency, fear responses, and functional impairment, to treat concurrent disorders, to prevent relapse and to build resilience capacity and improve quality of life (Berger et al., 2009).

2.1 Psychotherapy

Meta-analytic studies have demonstrated that trauma-focused cognitive behavioral therapies have large effect sizes in treating PTSD (Otto et al., 2003). Exposure therapy is useful in treating characteristic features of PTSD and is considered the best psychotherapy for PTSD treatment (Ballenger et al., 2004). This technique helps patients confront thoughts and situations related to their trauma in a safe environment in order to reduce anxiety and fear responses. Other techniques include stress inoculation training to teach anxiety management in order to cope with fear; cognitive therapy, designed to modify irrational interpretations of the trauma that are often the root of the negative emotions; and eye movement desensitization, the process of stimulating rapid eye movements simultaneous to image exposure. Trauma-focused cognitive behavioral therapy (CBT) uses some elements of these treatments (Seedat, Stein, & Carey, 2005). As discussed in the psychotherapy methods for TR-PTSD, refugees resistant to treatment often respond well to this form of treatment (see section 4.7).

2.2 Pharmacotherapy

Antidepressants are the standard first-line pharmacological approach in treating PTSD. Selective serotonin reuptake inhibitors (SSRIs) are the most studied family of antidepressant for the treatment of PTSD, with fluoxetine, sertraline and paroxetine being the most examined for this purpose. Sertraline and paroxetine have been approved by Federal Drug Administration (FDA) for the treatment of PTSD. These SSRIs have demonstrated short-term (6-12 weeks) effects in PTSD treatment, and if continued for longer (6-12 months) also reduce relapse rates (Asnis, Kohn, Henderson, & Brown, 2004). SSRIs block the serotonin transporter, thereby preventing the re-uptake of serotonin, increasing the amount of serotonin in the synapse. However, the mechanism(s) by which SSRIs achieve their beneficial effect in PTSD is not well understood.

Selective serotonin and norepinephrine reuptake inhibitors (SNRIs) have also been indicated in the treatment of PTSD (Asnis et al., 2004). One of the SSRIs, venlafaxine extended release (ER), has been evaluated in two randomized controlled trials (Davidson, Baldwin et al., 2006; Davidson, Rothbaum et al., 2006), and was well tolerated and effective for treating PTSD.

3. Definition of PTSD-treatment resistance

Although considered the first line of treatment, response rates to treatment with SSRIs are usually no higher than 60% and fewer than 30% of people achieve full relief (Berger et al., 2009). Response to antidepressant treatment is currently defined as a greater than 30% reduction in Clinician Administered PTSD Scale (CAPS) scores or a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impressions scale-Improvement item (CGI-I). Therefore, even those who respond partially to treatment may still meet the

criteria for PTSD at the end of treatment (Berger et al., 2009). The ultimate goal of treatment is remission.

Remission in PTSD can be defined as a CAPS score ≤ 20 . When determining if a patient is resistant to treatment, the initial diagnosis should be reviewed. Medication compliance, dosage, and duration of trial should be assessed (Bandelow et al., 2008). If after eight to 12 weeks the patient has not responded to the optimized dose, the medication should be changed. If the patient experiences a partial response, they may respond within another four to six weeks on the medication. In patients who are still unresponsive, trauma-focused cognitive-behavior therapy should be added (Bandelow et al., 2008).

Unfortunately, at this point, many patients are still refractory to treatment. An individual who, despite adequate treatment with antidepressants and cognitive behavioral therapy, still meets the criteria for PTSD is considered treatment-resistant. Additionally, some patients who experience partial response to treatment can still meet the criteria for a diagnosis of PTSD and are therefore also considered treatment-resistant. The definition of treatment resistance may vary across studies, but is generally the failure to fully respond or to respond at all to previous treatment, such as antidepressants and psychotherapy, after an appropriate trial period. There is little consensus on the next step in treatment.

Resistance to PTSD treatment can be associated with more severe cases of PTSD, the experience of multiple traumas, the type of trauma, other comorbid psychiatric disorders and gender, among other factors (Hamner, Robert, & Frueh, 2004). The additive effect of such factors manifests itself differently in civilian, combat-veteran and refugee populations. For example, civilian populations are most often responsive to antidepressants (Hamner et al., 2004), whereas, combat-veterans often have co-morbid psychiatric disorders (Hamner, 1997; Pivac & Kozaric-Kovacic, 2006), which can increase the severity of PTSD symptoms and the likelihood of treatment-resistance. Refugees commonly suffer from extreme forms of PTSD, often co-morbid with panic disorder. Among refugees, the prevalence of PTSD is estimated to range from 10-86%, a prevalence rate much higher than that of the general population. The nature of PTSD in refugee populations is often more severe due to prolonged exposure to traumatic events, pre-, post- or during migration (Boynton, Bentley, Strachan, Barbato, & Raskind, 2009). As such, refugees often have forms of PTSD that are not responsive to standard treatment with SSRIs.

Due to additional cultural issues and barriers with refugees, cognitive behavioral therapy is recommended for treatment refractoriness and can be adjusted to meet the specific needs of different cultures (Hinton et al., 2005; Hinton, Hofmann, Rivera, Otto, & Pollack, 2011; Hinton et al., 2004; Otto et al., 2003).

4. Pharmacotherapy and psychotherapy for TR-PTSD

After treatment-resistance is determined, there are several proposed pharmacotherapeutic and psychotherapeutic approaches. Though the literature base is small, several randomized controlled trials (RCTs), open-label trials and case series exist that evaluate the efficacy of alternative treatments. As noted above, the criteria for response can be based on the CAPS score or the CGI-I score. Previous studies have differed in use of drug treatments for monotherapy or as add-on therapy, trial duration and goals of treatment. This section reviews each class of drug and the evidence-base (or lack thereof) for efficacy in TR-PTSD.

4.1 Antidepressants

SSRIs and SNRIs are considered to be first line treatments for PTSD. Only SNRIs have demonstrated preliminary efficacy in treatment specific to cases of treatment-resistance. Duloxetine is another SNRI that has been evaluated for its efficacy in treating refractory-PTSD. In an open-label trial, duloxetine has demonstrated efficacy for treating TR-PTSD in mostly male and military samples; however, further investigation is still required.

4.1.1 Duloxetine

As a dual reuptake inhibitor and approved treatment for major depressive disorder (MDD), duloxetine was evaluated for its efficacy for treatment of PTSD. In an eight-week open label trial, Walderhaug et al (2010) treated 21 male patients with both refractory PTSD and comorbid MDD. Duloxetine was administered as monotherapy with a dose of 60-120mg/day. All patients were deemed treatment-resistant by having failed at least two previous treatments with antidepressants. On the primary outcome measure, PCL-C, scores improved significantly. Scores also improved on the HAM-A, MADRS and CGI-S. At the end of the eight weeks, 42% of the patients (N=8/21) responded to treatment and 21% (N=4/21) were considered to have reached remission criteria. Overall, duloxetine was found to decrease PTSD and concurrent MDD symptoms, and improve upon quality of sleep.

4.1.2 Other antidepressants

Only a small literature exists about the use of other antidepressants such as TCAs and MAOIs for non-refractory PTSD, and with no consistent positive results. The only antidepressant to be tested in a treatment-resistant sample was nefazodone (Gillin et al., 2001; Zisook et al., 2000). While positive effects were seen in the nefazodone evaluations, it was taken off the market in Canada and the United States due to adverse effects on the liver.

4.2 Atypical antipsychotics

Psychotic symptoms can be quite prevalent in those with PTSD, especially in veterans with combat exposure (Stein, Kline, & Matloff, 2002). The prevalence of psychosis in veterans with PTSD is estimated to range from 30-40% (M. B. Hamner, 1997). Psychotic symptoms are often associated with more severe symptoms that are not affected by the standard treatment with SSRIs or other antidepressants (Pae et al., 2008; Sareen, Cox, Goodwin, & Asmundson, 2005). It is suggested that PTSD affects serotonergic and dopaminergic pathways, both of which can be acted on by atypical antipsychotics (M. B. Hamner, Faldowski et al., 2003). There is also some indication that PTSD can affect alpha-adrenergic receptors as well, which can also be acted on by some atypical antipsychotics. Some activities of these drugs include, D₂, 5-HT₂ and alpha₁ adrenergic receptor antagonism. Certain drugs also have an antihistaminic role, helping with some of the sleep-disturbances accompanying PTSD (Ravindran & Stein, 2009). As such, atypical antipsychotics have been utilized as a monotherapy and as adjunctive treatment for PTSD, with or without psychotic symptoms, with most evidence supporting the use of them as an adjunctive therapy.

Three RCTs (see Table 1), eight open-label trials and multiple case series were identified for the use of atypical antipsychotics in the treatment of TR-PTSD. The following is a summary of the studies on atypical antipsychotics:

Name of Anti-psychotic		Definition of treatment-resistance	Dose (mg/day) [mean]	Trial (wks)	Existing therapy	Outcomes	Findings (as compared to control groups)
Olanzapine	Stein <i>et al.</i> , 2002 (n=19)	Only minimal response to 12 weeks of SSRIs	10 [15]	8	SSRIs	1. CAPS total score 2. CES-D 3. PSQI 4. CGI -I	- Improved on CAPS, CES-D, PSQI - No significant differences between control and treatment group on CGI-I
Risperidone	Hamner <i>et al.</i> , 2003 (n=37)	Only partially responsive to current medication	1-6 [Final dose: 2.5 ± 1.25]	5	Antide-pressants	1. PANSS total score 2. PANSS subscale scores 3. CAPS total score 4. CAPS subscale scores	- Modest results in treatment of psychotic and re-experiencing symptoms - Decrease in PANSS
	Bartzokis <i>et al.</i> , 2004 (n=65)	Patients deemed “probably treatment resistant”	1-3	16	Antide-pressants	1. CAPS total score 2. CAPS subscale scores 3. PANSS-P 4. HAM-A 5. HAM-D	- significant improvement on all measures - reduced PTSD symptoms, symptoms clusters (anxiety, psychosis, depression)
	Rothbaum <i>et al.</i> , 2008 (n=20)	Unresponsi ve to SSRIs over the past year	0.5-2 mg/day.	8	SSRIs	1. PANSS 2. CAPS total score 3. CAPS subscale score 4. DTS 5. CGI	- Improved on DTS scores -improved on CGI-I scores -No change in CAPS

Table 1. **Summary of RCTs of atypical antipsychotics for treatment of TR-PTSD.** CAPS: Clinician Administered PTSD Scale; CGI: Clinical Global Improvement Scale; PNASS: Positive and Negative Syndrome Scale; CES-D: Center for Epidemiologic Studies Depression Scale; PSQI: Pittsburgh Sleep Quality Index; DTS: Davidson Trauma Scale

4.2.1 Olanzapine

Olanzapine has high affinity for D₂ dopamine receptors and 5-HT₂ serotonin receptors (Jakovljevic, Sagud, & Mihaljevic-Peles, 2003) as well as affinities for adrenergic, histaminergic and muscarinic receptors (Butterfield et al., 2001). Olanzapine, with its sedative activities, has the potential to treat sleep disturbances accompanied with PTSD (Stein et al., 2002).

One RCT (Stein et al., 2002) shows beneficial results for the use of olanzapine in treating refractory PTSD over an 8-week trial. 19 patients who only minimally responded to 12 weeks of SSRIs were considered treatment-resistant. Stein et al. (2002) found that when using olanzapine (mean dose 15 mg/day) in conjunction with previously indicated SSRIs at a maximally tolerated dose, scores on CAPS, CES-D and PSQI measures significantly improved as compared to individuals who were given a placebo in conjunction with SSRIs. Based on the CGI-I measure, the percentage of responders was not significantly different between the treatment (30%) and placebo (11%) groups. Although a small RCT, this study shows olanzapine to be effective in treating individuals with TR-PTSD, and in particular, treatment-resistant sleep symptoms. One open-label trial (Pivac, Kozaric-Kovacic, & Much-Seler, 2004) shows the efficacy of olanzapine in reducing PTSD symptoms. Pivac et al., (2004) defined treatment resistance as those patients who were unresponsive with SSRIs for six to 12 months prior to the study. In a series of case reports (Jakovljevic et al., 2003), five patients who had been given various psychotropic medications for years were treated additionally with olanzapine. Sleep disturbance symptoms in these patients were much improved with adjunctive olanzapine treatment. Olanzapine appears to be an effective adjunctive treatment for refractory PTSD.

4.2.2 Risperidone

Risperidone has affinity for 5-HT_{2A}, 5-HT₇, D₂, and alpha-1 and 2 receptors. As such, risperidone has the capacity to reduce positive and negative symptoms of PTSD, such as, delusions, hallucinations, thought disorder, hostility, social and emotional withdrawal and aggression, among others (Kozaric-Kovacic, Pivac, Muck-Seler, & Rothbaum, 2005). Two RCTs (Hamner, Faldowski et al., 2003; Bartzokis et al., 2004) and two open-label trials (David, De Faria, & Mellman, 2006; Kozaric-Kovacic et al., 2005) demonstrate the positive effect of risperidone in the treatment of refractory PTSD. However, Rothbaum et al (2005) failed to find any benefit of risperidone on the primary CAPS outcome. Treatment resistance includes criteria such as, unresponsive to SSRIs over the past year (Bartzokis et al., 2004; Kozaric-Kovacic et al., 2005; Rothbaum et al., 2008) and as only partially responsive to current medications (David et al., 2006; M. B. Hamner, Faldowski et al., 2003). Risperidone is evaluated in conjunction with participants' regular doses of either SSRIs (Rothbaum et al., 2008) or all antidepressants (M. B. Hamner, Faldowski et al., 2003). Average daily doses of risperidone ranged between 1.9-2.5mg/day for 5-16 weeks. The percentage of responders to risperidone compared to the placebo was not recorded. Modest results were found for the combination of antidepressants and risperidone in treatment of the psychotic and re-experiencing symptoms of PTSD. (Hamner, Faldowski et al., 2003). The open label trials were consistent in showing the benefit of adjunctive treatment and monotherapy treatment with risperidone. One study in particular (David et al., 2006) specifically showed risperidone to be effective in treating the sleep symptoms accompanying PTSD. In summary, risperidone has shown some promise for TR-PTSD, but larger, more rigorous RCTs are needed for confirmation.

4.2.3 Quetiapine

Quetiapine demonstrates alpha-1 blocking activity and has low side effects (Kozaric-Kovacic & Pivac, 2007). Quetiapine use for treating refractory PTSD is shown to be effective in three open-label trials (Ahearn, Mussey, Johnson, Krohn, & Krahn, 2006; M. B. Hamner, Deitsch, Brodrick, Ulmer, & Lorberbaum, 2003; Kozaric-Kovacic & Pivac, 2007). Two studies examine quetiapine as an adjunctive therapy to antidepressants or other psychotropics (Hamner, Deitsch et al., 2003) or with SSRIs (Ahearn et al., 2006), whereas Kozaric-Kovacic and Pivac (2007) examine quetiapine as a monotherapy. Resistance to treatment was defined as no change in CAPS scores after two 8-week trials with different antidepressants (Kozaric-Kovacic & Pivac, 2007), incomplete responsiveness to treatment (Hamner, Deitsch et al., 2003) or as still experiencing PTSD symptoms despite being on a stable dose of SSRIs (Ahearn et al., 2006). The CAPS total and subscores are used as primary outcomes in all open label studies. Before treatment, CAPS scores, on average were above 80. All studies demonstrated a significant reduction in CAPS total scores and CAPS subscale scores (avoidance, re-experiencing and hyperarousal). Ahearn et al. (2006) found an average final CAPS score of 46, representing a 42% decrease in symptom severity. All three subscales, B, C and D, showed significant reduction as well (23 to 10, 27 to 23 and 26 to 14, respectively). Treatment doses across all three trials ranged from 25 mg per day to 400 mg per day (mean dose ranging from 100 ± 70 mg/day to 335.75 mg/day). The open-label trials indicate the efficacy of quetiapine for TR-PTSD; however, larger and more rigorous studies are required for conclusive results.

4.2.4 Fluphenazine

One open label study reports on the effectiveness of fluphenazine as a treatment for refractory PTSD as compared to olanzapine (Pivac et al., 2004). Patients included were all unresponsive to six to 12 months of prior treatment with SSRIs. The six-week trial using 5-10 mg/day of fluphenazine as a monotherapy showed effectiveness of the drug in reducing re-experiencing, avoidance and hyperarousal symptoms; however, olanzapine had a greater effect on both avoidance and hyperarousal symptoms. Fluphenazine was effective in treating the cluster symptoms of PTSD in a treatment resistant sample. However, to date, there is not enough evidence to be conclusive as to the utility of fluphenazine or other typical antipsychotics in TR-PTSD.

4.2.5 Clozapine

One open-label study indicates that clozapine may be effective in treating PTSD with psychotic symptoms (Wheatly, Plant, Reader, Brown, & Cahill, 2004). Six participants, whose psychotic features were resistant to at least two conventional antipsychotics, were given between 600 and 800 mg/day of clozapine. Four participants responded either significantly or moderately to the treatment, whereas two others remained uncertain of the effect. Due to the open-label design and small sample size, there is not yet enough evidence to conclude that clozapine is effective for treatment refractory PTSD.

4.2.6 Aripiprazole

Aripiprazole is a 5-HT_{2A} antagonist with partial agonist effects on the 5-HT_{1A} and D₂ receptors contributing to a reduction in anxiety. Two open-label trials demonstrate the potential effectiveness of aripiprazole in treating refractory-PTSD. In a 12-week trial,

participants were given a mean dose of 12.95 mg/day of the drug as a monotherapy treatment (Villarreal et al., 2007). Of the 22 participants, 15 of them (68%) had previously been unresponsive to two or more antidepressants. By the end of the trial, 14 people (64%) responded to treatment, defined as a minimum of 20% improvement on the CAPS scale, and two participants remitted. Of the 14 responders, twelve participants had a CGI-I score of very much, or much improved. In a second 12-week trial, a flexible dose (15-30 mg/day) of the drug was given adjunctively to the 20 participants (Robert, Hamner, Durkalski, Brown, & Ulmer, 2009). Of these 20 participants, 85% of them had previously been treated with an average of 1.5 antidepressants trials, but were still experiencing significant PTSD symptoms. Based on the response criteria of a minimal decrease in CAPS score by 20%, 53% of the sample responded to treatment. In addition, a recent chart review of veterans with both PTSD and comorbid depression that received this drug in an open-label fashion for 12 weeks experienced a reduction in both PTSD and depression severity. Treatment resistance was defined as being minimally or partially responsive to previous medication (Richardson, Fikretoglu, Liu, & McIntosh, 2011). These findings suggest that aripiprazole may be effective in treating PTSD in those who are considered treatment resistant; however, further and more rigorous evaluation of the drug is required.

Based on the evidence, it appears that olanzapine and risperidone are the most effective atypical antipsychotics for the treatment of refractory PTSD. The study of atypical antipsychotics in treatment of refractory PTSD is promising, however more research is needed, including larger sample sizes and more double blind randomized controlled trials.

4.3 Anti-adrenergic agents

Prolonged duration of adrenergic activation heightens the risk of developing PTSD. Often those with PTSD have an altered regulation of their adrenergic system. Anti-adrenergic agents may therefore be able to reverse or minimize the development and/or symptoms of PTSD (Marmar, Neylan, & Schoenfeld, 2002).

The following drugs have been evaluated in relation to PTSD. Three RCTs (see Table 2), four open-label trials and two case series have examined anti-adrenergic agents in the context of reducing sleep disturbances, preventing PTSD development and reducing hyper-arousal symptoms.

4.3.1 Prazosin

Nightmares and other sleep disturbance symptoms are common in combat-related traumas, and are often symptoms that are resistant to treatment. Prazosin is an anti-adrenergic agent that has been specifically evaluated in such individuals where nightmare symptoms are not responding (Raskind et al., 2002). Prazosin is a selective alpha-1 antagonist. It is proposed that alpha-1 receptor stimulation is associated with sleep disturbances and stress-linked disruptions in cognitive processing, both evident in PTSD. Therefore, prazosin, with its blocking effects, might be useful in reducing the sleep-related symptoms of PTSD (Ravindran & Stein, 2009).

Two RCTs test the efficacy of prazosin as augmentative therapy for reducing sleep disturbance symptoms associated with PTSD in combat veterans (Raskind et al., 2007; Raskind et al., 2003). Ten combat veterans with refractory PTSD participated in the 20-week, double blind crossover design (Raskind et al., 2003). Refractory PTSD symptoms were defined by frequent and severe trauma-related nightmares (>6 on CAPS), despite treatment

Name of Anti-adrenergic		Definition of Treatment Resistance	Dose (mg/ day) [Mean]	Trial (wks)	Existing Therapy	Outcomes	Findings (as compared to control groups)
Prazosin	Raskind et al., 2003 (n=10)	Frequent and severe trauma-related nightmares (>6 on CAPS), despite treatment with a stable dose of psychoactive medications.	1-10 [9.5]	20	Augmentation	1. CAPS 2. CGI-C	- Improved sleep and nightmare symptoms - Improved CGI-C score
	Raskind et al., 2007 (n=40)	Frequent and severe trauma-related nightmares (>6 on CAPS), despite treatment with a stable dose of psychoactive medications.	1-15 [13.3± 3]	8	Augmentation	1. CAPS 2. CGI 3. PSQI	- Reduced trauma-related nightmares and improved sleep - Improved Global Clinical Status
Guanfacine	Neylan et al., 2006 (n=63)	Participants taking no medication, or continued to meet the criteria for PTSD even though they were on a stable dose of medication	1-3 [2.4]	8	Augmentation	1. CAPS 2. IES-R 3. SQI	- No effect on PTSD symptoms, sleep quality or general mood

Table 2. **Summary of RCTs of antiadrenergics for treatment of Post-traumatic Stress Disorder.** CAPS: Clinician Administered PTSD Scale; CGI: Clinical Global Improvement Scale; PSQI: Pittsburgh Sleep Quality Index; PCL-C: Posttraumatic Stress Disorder checklist-civilian version; IES-R: Impact event scale revised; SQI: subjective sleep quality.

with a stable dose of psychoactive medications. A mean dose of 9.5mg/day of prazosin or placebo was given before bed. On outcome measures, sleep disturbances, nightmares and CGI-C, those taking prazosin showed more improvement as compared to the control group. The drug group also showed reduced symptoms in all three PTSD symptom clusters. In

their eight-week RCT (Raskind et al., 2007), a mean dose of 13.3mg/day of prazosin or placebo was administered. All participants had chronic nightmares that were unresponsive or only partially responsive to prior treatment. Prazosin greatly improved PTSD-related nightmares, sleep quality and CGI-C scores, as compared with the placebo. The drug group experienced a decrease of 50% in recurring, distressing dreams, whereas the placebo group only experienced a decrease in 15%. These two studies show prazosin to be effective in treating the sleep disturbance and nightmare symptoms associated with PTSD in combat veterans. Three open label studies are also consistent in demonstrating the effectiveness of prazosin in treating sleep disturbance symptoms associated with PTSD (Peskind, Bonner, Hoff, & Raskind, 2003; Taylor & Raskind, 2002; Taylor et al., 2006). Taylor et al (2006) demonstrated that in those civilians that continued to experience daytime PTSD symptoms even though on a stable dose of nighttime prazosin, it was beneficial to add a daytime dose (mean dose 3.2mg/day) as well. Raskind et al (2002) retrospectively examined combat veterans with PTSD who had been treated with prazosin. All participants had chronic trauma-related nightmares (score of 5-8 on CAPS recurrent distressing dreams item), despite treatment with stable dose of medication. Primary outcome measures were CAPS and CGI-C scores. In those who completed at least eight-weeks of prazosin (mean dose 9.6mg/day), recurring, distressing dreams were significantly reduced. In those that were prescribed prazosin but did not comply, there was no such change. There is a good level of evidence to support the use of prazosin in TR-PTSD patients with sleep disturbance and nightmare symptoms.

4.3.2 Guanfacine

Guanfacine acts as an alpha-2 adrenergic agonist (Ravindran & Stein, 2009), and as such is proposed as a mechanism for reducing hyper-arousal symptoms associated with PTSD. In an eight-week double blind, randomized controlled trial, 63 veterans with TR-PTSD received either an average dose of 2.4mg/day of guanfacine or of placebo (Neylan et al., 2006). Included participants were either taking no medication, or continued to meet the criteria for PTSD even though they were on a stable dose of medication. Guanfacine showed a small but statistically significant effect in reducing CAPS scores, as compared to the placebo group, as well as a decrease in the average total IES-R score. After eight weeks, the drug was no more effective than the placebo in reducing PTSD symptoms. In addition, those who were given guanfacine experienced high rates of adverse effects, such as dry mouth, light-headedness and a drop in blood pressure. Based on the results of this trial, guanfacine is not suggested to benefit individuals with PTSD.

4.3.3 Clonidine

Similar to the effect of guanfacine, clonidine, an alpha-2 adrenergic agonist, blocks the alpha-2 receptors in areas with high concentrations of norepinephrine, thus reducing sympathetic tone. As such, it is hypothesized that the drug can have beneficial effects on the hyper-arousal symptoms exhibited in PTSD (Ravindran & Stein, 2009). In an open-clinical trial (Harmon & Riggs, 1996), pre-school children with PTSD were treated with clonidine (average dose, once stabilized, 0.1-0.105mg/day). Children were only included in this study if they had been unresponsive to at least one, but often several months of behavioral treatment. Based on teacher and physician opinion, all children experienced a decrease in aggressive behavior, and 71% of the children exhibited decreased impulsivity,

hypervigilance, anxiety, temper-tantrums, oppositional behavior and sleep disturbances. After trying out many different drugs, Kinzie and Leung (1989) found TCAs most effective in relieving PTSD symptoms. Cambodian refugees (N=12) with PTSD were treated with a combination of imipramine (maximum dose 150mg/day) and clonidine (0.1-0.6mg/day). Only two patients showed enough improvement to no longer meet the criteria of PTSD, however most showed reduced symptoms, such as, improved sleep, startle reactions and avoidance. This study indicates the usefulness of the TCA-clonidine combination in reducing PTSD symptoms; however, further RCTs are needed to investigate.

Prazosin has been the most rigorously evaluated anti-adrenergic agent that has shown benefit in treating refractory-PTSD patients. Further evaluation of clonidine in the future may provide additional insight into its use.

4.4 Anticonvulsants

Kindling, the process whereby repeated sub threshold stimulation to the central nervous system (CNS), makes the nerves more sensitive to stimuli. This phenomenon has been shown to occur in the amygdala and limbic regions of the CNS, areas linked to fear and stress. Anticonvulsants, known for their anti-kindling properties, are therefore proposed as a possible treatment for PTSD (Berger et al., 2009).

There have been numerous studies, including, one RCT, three open label trials and several case studies, examining the potential efficacy of anticonvulsants in treating refractory PTSD. Such anticonvulsant drugs include, topiramate, valproic acid, tiagabine and levetiracetam. The following is a summary of the existing literature on anticonvulsants in the treatment of TR-PTSD.

4.4.1 Topiramate

Topiramate has several different mechanisms of operation. Topiramate blocks calcium and sodium channels, increasing the activity of GABA, inhibiting the activity of carbonic anhydrase enzyme and blocking the AMPA receptor. Topiramate's anti-kindling properties may block certain pathways involved in PTSD (Andrus & Gilbert, 2010).

One RCT testing the efficacy of topiramate in treating PTSD shows potential benefit. In a 12-week adjunctive therapy, double blind, randomized control trial, 67 patients who were being treated with psychotropic medications, but experiencing no response were included. There was a significant improvement between those combat veterans receiving the drug (50-500mg/day) and those receiving the placebo (Akuchekian & Amanat, 2004). PTSD symptoms of re-experiencing, sleep disturbances, irritability, anger, difficulty recalling, and startle reaction were reduced in the experimental group. In a case series (Berlant, 2001), when previous medications were ineffective, topiramate was reported to help with re-experiencing symptoms, such as nightmares and intrusive flashbacks. There is suggestion that topiramate, as an anticonvulsant agent, may be effective in treatment-resistant individuals with PTSD; however, the findings of the RCT need to be replicated and additional investigation is required.

4.4.2 Valproic acid (Valproate and Divalproex)

Valproic acid and its derivatives (valproate and divalproex) have been commonly studied as treatments for refractory PTSD. Valproic acid increases the amount of GABA, a neurotransmitter (Adamou, Puchalska, Plummer, & Hale, 2007) and enhances the inhibition

of gamma-aminobutyric acid. Through these mechanisms, it is hypothesized that valproic acid reduces intrusion and hyperarousal symptoms associated with PTSD (Otte, Wiedemann, Yassouridis, & Kellner, 2004).

One open label study has been conducted examining the use of valproate as an effective treatment for PTSD. Otte et al (2004) treated ten civilians with valproate monotherapy in an eight-week open label trial. The average duration of PTSD for the participants was 8.6 ± 8.7 years, and previous, ineffective treatments included, antidepressants, antipsychotics and CBT. The drug was initiated at 250mg/day and was titrated incrementally up to 2000mg/day, as tolerated (mean dose 1400 ± 380 mg/day). This trial found no significant improvement in PTSD symptoms in the civilian population.

The use of divalproex in treating refractory PTSD has shown beneficial results. One open label study (Goldberg, Cloitre, Whiteside, & Han, 2003) supports the use of divalproex in treating patients with PTSD related to childhood abuse. All participants in this study were considered treatment-resistant on the basis of continued PTSD symptoms in the past three months, regardless of receiving treatment. A mean dose of 1500mg/day was given to each of the seven participants. Significant improvement was seen in all clusters of PTSD symptoms as well as in general symptom severity.

The mixed results of the evaluations of the valproic acid derivatives warrant further research, including larger studies.

4.4.3 Tiagabine

Tiagabine is a selective GABA reuptake inhibitor, and as such, increases the extracellular supply of GABA (Connor, Davidson, Weisler, Zhang, & Abraham, 2006). The increased availability of GABA in the neural cleft interacts with postsynaptic GABA receptors, producing quick inhibition, resulting in a potential treatment mechanism for PTSD.

In a case series, women whose PTSD was still symptomatic despite treatment with a stable dose of medication, were treated with an adjunctive dose of tiagabine (Taylor, 2003). Within two weeks of the treatment, six out of seven of the patients showed improvement when given a mean dose of 8mg/day of the drug. However, in a 12-week RCT Davidson et al (2007) administered between four and 16mg/day of tiagabine or placebo to 232 patients. No significant differences were found between the treatment and control group on the CAPS scale or on other measures. This study demonstrates that tiagabine was clearly ineffective in reducing PTSD symptoms. This study however, excluded individuals who were unresponsive to at least two or more previously pharmacological treatments for PTSD. Therefore, it is unlikely for this treatment to be effective in a treatment resistant sample; however, this has not been investigated.

4.4.4 Levetiracetam

Levetiracetam reduces signal transmission through high voltage calcium channels. This drug might also effect the functioning of the SV2A synaptic vesicle protein. Animal models show that levetiracetam may reduce the anxiety induced by withdrawal from benzodiazepines (Kinrys, Wygant, Pardo, & Melo, 2006).

In a retrospective study, Kinrys et al (2006) treated non-responding PTSD patients with levetiracetam in an adjunctive therapy fashion. A mean dose of 1967 ± 650 mg/day was given to patients for an average of 9.7 ± 3.7 weeks. Significant improvements were seen in PCL-C, CGI-S and HAM-A scores. Thirteen patients (56%) were characterized as

responders, and 6 patients (26%) were characterized as remitters. No patients discontinued treatment due to adverse effects. These findings are inconclusive pending further research that must include RCTs.

Based on the literature to date, there is not enough evidence to recommend the use of anticonvulsants for treating TR-PTSD.

4.5 Mood stabilizers

4.5.1 Lithium carbonate

Lithium stimulates serotonin synthesis and increases the sensitivity of pre- and post-synaptic receptors to serotonin. These mechanisms may be responsible for the ability of lithium to reduce aggression (Forster, Schoenfeld, Marmar, & Lang, 1995).

In a case series Kitchner and Greenstein (1985) reported on the effect of low dose lithium carbonate (300-600 mg/day) in treating the PTSD-related anger, irritability, anxiety and sleep disturbance symptoms in individuals who were resistant to other treatment (tranquilizers, antidepressants, hypnotics and psychotherapy). Over three to 12 months, adjunctive treatment with lithium was effective in treating these treatment-resistant symptoms. No further and more up-to-date studies on lithium treatment of refractory PTSD patients were found in the literature. As a result, lithium may be an effective treatment for specific symptoms of TR-PTSD, but more rigorous evaluation is necessary.

4.6 Anxiolytics

Benzodiazepines exert their effect on the GABA benzodiazepine receptor, further increasing the activity of inhibitory neurotransmitter, GABA. Generally, this results in sedation, anxiolysis, muscle relaxation, as well as decreased arousal (Ravindran & Stein, 2009). Benzodiazepines have not been evaluated in a treatment-resistant sample. On the other hand, buspirone, a non-benzodiazepine anxiolytic acts similarly and is evaluated for efficacy in treating refractory PTSD.

Only one clinical series was identified in the literature to deal with treatment-resistant individuals specifically.

4.6.1 Buspirone

In a clinical series (Hamner, Ulmer, & Horne, 1997), patients who were completely unresponsive or only partially responsive to prior medication were additionally treated with buspirone. Of the participants, 73% (N= 11/14) responded positively to buspirone augmentation (mean dose 40mg/day). Randomized trials are needed to further examine the effectiveness of buspirone.

4.7 Cognitive Behavioral Therapy (CBT)

Several studies have found cognitive behavioral therapy (CBT) to be effective for treatment-resistant refugees. Otto et al (2003) randomly assigned ten women to either receive sertraline (mean dose 125mg/day) or sertraline (mean dose 100mg/day) plus CBT. All women had previously failed to respond to a combination of clonazepam (0.5-1mg/day) plus an SSRI other than sertraline. CBT focused on information, exposure and cognitive modification. The combination of sertraline and CBT was more effective than sertraline alone. Hinton et al (2004) randomly assigned Vietnamese refugees with PTSD and concurrent panic attacks to two different cohorts, one to receive treatment immediately, and the other to be on the wait-

list. All included participants still met criteria for PTSD diagnosis despite treatment with a stable dose of SSRIs and supportive counseling. CBT was adapted to be culturally appropriate. Significant improvements were seen on all outcome measures, demonstrating the efficacy of culturally adapted CBT. A trial with Cambodian refugees with TR-PTSD and comorbid panic attacks (Hinton et al., 2005) likewise found benefit of a culturally adapted CBT program. In the randomized controlled trial, Hinton et al (2009) studied the mechanism behind the efficacy for CBT in Cambodian refugees. Patients receiving the treatment showed much greater improvement on one physiological measure and on all psychometric measures. In addition, those in the waitlist group significantly improved once they too received treatment. The study found the severity of PTSD to be mediated by orthostatic panic and emotion regulation. The vagal tone and emotional regulation ability is improved by CBT, suggesting a decrease in vagal tone to be associated with PTSD and orthostatic panic among refugees, as well as with emotional regulation ability. In a culturally adapted, 14-week, CBT trial of Latino women with TR-PTSD (Hinton et al., 2011), significant reduction in PTSD symptoms was again demonstrated. Treatment resistance was defined as still meeting PTSD criteria despite receiving supportive therapy and a maximally tolerated dose of SSRIs for at least six months. These few studies demonstrate the ability of culturally adapted CBT to be an effective treatment for refugees with PTSD who are not responding to first line treatment.

4.8 Alternative treatments

Multiple alternative treatments have been evaluated for their uses in treating refractory PTSD. Two RCTs have been performed looking at different methods for treatment.

Kaplan et al (1996) evaluated the use of inositol in a double-blind randomized, controlled cross-over trial. Inositol is a second messenger that exerts its effect over neurotransmitters such as serotonin. It has been shown to have antidepressant and anti-panic properties, and is therefore proposed to also help alleviate PTSD symptoms. Included participants were those who had no response or only partial response to a trial of antidepressants or other treatment, or had refused treatment with medication. Participants were treated with either 12g/day of inositol or of placebo only. Response to treatment was based on the IES, and its two subscales for avoidance and intrusion. Overall, no significant differences were found between treatment and placebo groups in overall IES score, either subscale or on the Hamilton depression and anxiety scales. This study shows inositol to have no effect on TR-PTSD.

A second RCT evaluated the use of $\pm$ 3,4-methylenedioxymethamphetamine (MDMA) for TR-PTSD (Mithoefer, Wagner, Mithoefer, Jerome, & Doblin, 2010). In the past, MDMA has been shown to reduce fear, while maintaining a state of alertness and is therefore proposed to be helpful in conjunction with psychotherapy. Individuals who were resistant to both psychotherapy and psychopharmacology were randomized to receive either MDMA or placebo in two 8-hour experimental psychotherapy sessions. The CAPS was used to indicate response to treatment. In the treatment-group, 83% (N= 10/12) individuals responded, whereas, only 25% (N=2/8) in the placebo-group responded. No serious adverse effects were seen. This is an interesting proof-of-concept and the role of this drug in the treatment of PTSD remains to be determined.

Abramowitz and Lichtenberg (2010) conducted a prospective open study on the efficacy of a new hypnotic technique for TR-PTSD. The new technique, hypnotherapeutic olfactory conditioning (HOC), consists of six 1.5 hour sessions per week where the patient is taught to

use a pleasant-smelling scent to help them re-enter and remain calm in situations that trigger anxiety and panic. All participants in this study had continual PTSD symptoms and olfactory trigger components despite prior treatment. The IES-R, BDI and Dissociative Experiences Scale were used to assess the treatment. At the end of the six weeks, a significant reduction was seen in PTSD symptoms, depression and dissociative experiences. Response to treatment was indicated by a 50% decrease in IES-R scores. Of the participants, 58% responded. In those who have olfactory trigger components to their PTSD, HOC may be an effective treatment.

Nabilone, a synthetic cannabinoid substance was also evaluated as a potential treatment for individuals whose PTSD-related nightmares were resistant to treatment for at least two years (Fraser, 2009). In this open label clinical trial, nabilone (mean dose 0.5mg/day) was added to the medication regiment of 47 patients. Thirty-four of the patients (72%) experienced complete or significant reductions in their nightmares. Nabilone may be effective for treatment-resistant nightmares, but its role in treatment of TR-PTSD is cautioned as it is still inconclusive.

5. Implications for clinicians

While SSRIs and cognitive behavioral therapy have been deemed the prime treatment for PTSD, many do not respond. There are many different factors contributing to treatment-resistance and it varies between individuals. As such, there is limited evidence-based research on the obvious next step for treatment of these patients. As evidenced by the array of pharmacological and psychotherapeutic methods for treatment, little consensus exists. Further research is required on the better strategies for treating individuals with refractory-PTSD.

Although there is no treatment algorithm for the management of TR-PTSD, since PTSD commonly presents with comorbidities it is essential that the clinician confirms the diagnosis and assesses treatment adherence in order to confirm treatment resistance. For example, to aggressively treat the comorbidities that are often present in TR-PTSD, such as treating major depression and addiction.

A clinician can also make use of current guidelines to aggressively treat and manage specific comorbidity, which might have contributed to the treatment resistance. According to updated guidelines for treating PTSD (VA/DoD, 2010), the choice of treatment should be based on symptom severity and all treatments should be evidence-based and within the clinician's capabilities to provide. When beginning pharmacotherapy for PTSD, clinicians should initiate a monotherapy trial with an optimized dose of first-line medication. An optimized dose takes into account the outcomes of the medication, the dose and the time until response. If the patient exhibits some response, the medication should be continued, unless the drug is not well tolerated. However, if the patient exhibits no response by approximately eight weeks, the dose should be increased, or the medication should be changed or augmented. The patient's adherence to the medication should be consistently assessed.

Based on the available evidence, when a first-line treatment (SSRI, SNRI) is not effective, switching to another antidepressant or another class of medication should be considered. The use of the anti-adrenergic agent, guanfacine, and anticonvulsants are not recommended as a monotherapeutic treatment for PTSD.

If switching medications does not elicit a response, augmenting the first-line treatment with another class of medication has demonstrated effectiveness. There is at present limited

evidence that augmentation with atypical antipsychotics, risperidone, olanzapine or quetiapine can be effective for TR-PTSD; these agents can be tried when appropriate. The evidence for treatment with adjunctive anticonvulsant therapy is mixed and therefore not conclusive at this time.

When choosing which medication to switch to or to augment with, it is important to consider which PTSD symptoms the patient is experiencing. For those patients experiencing TR-PTSD sleep disturbances, prazosin has demonstrated effectiveness, particularly in a combat-veteran population where these symptoms are common. Psychotic features are also often associated with combat-related PTSD, for which augmenting with atypical antipsychotics may be efficacious.

While only two drugs (sertraline and paroxetine) are FDA approved for treating PTSD, many other drugs have evidence in treating specific symptoms of PTSD or commonly comorbid conditions. Some of the drugs discussed in this chapter, such as, olanzapine, risperidone and prazosin have been rigorously tested and demonstrated positive effects on PTSD symptoms. Other drugs have shown some benefit for PTSD symptoms, yet lack the rigorous evaluation needed for a recommendation at this time.

Due to the limited literature base and multitude of options, it may be difficult for the clinician to determine the best course of action. Today, we are still unable to draw a conclusion. Although remission is not always possible, it is important to maintain and promote hope in patients who continue to be symptomatic as significant symptom reduction and improve quality of life are possible with treatment. A better understanding of the physiological and neurobiological underpinnings of PTSD will be essential to developing new and better treatments for PTSD. This greater understanding may also help us to prevent treatment-resistance by treating the PTSD earlier and more effectively. We can also do this by addressing not only those affected with PTSD, but those who have higher risk factors for being exposed to trauma and developing treatment-resistance.

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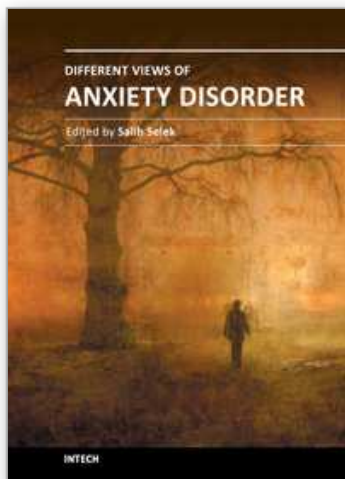
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Anxiety, whether an illness or emotion, is a term with historical roots even in the Bible, but it was not popular until the modern age. Today, we can group, diagnose and treat several anxiety disorders to an extent, but the assessment of symptoms and severity, dealing with resistant conditions, new treatment modalities and specific patient population, such as children, are still the challenging aspects of anxiety disorders. This book intends to present anxiety disorders from a different view and discuss a wide variety of topics in anxiety from a multidimensional approach. This Open Access book addresses not only psychiatrists but also a broad range of specialists, including psychologists, neuroscientists and other mental health professionals.

How to reference

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InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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