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## Clinical Psychology Review

Emerging treatments for PTSD<sup>☆</sup>Judith Cukor<sup>a,\*</sup>, Josh Spitalnick<sup>b</sup>, JoAnn Difede<sup>a</sup>, Albert Rizzo<sup>c</sup>, Barbara O. Rothbaum<sup>d</sup><sup>a</sup> Weill Cornell Medical College, 525 East 68th Street, Box 200, New York, NY 10065, USA<sup>b</sup> Virtually Better, Inc., 2440 Lawrenceville Hwy, Suite 200, Decatur, GA 30033, USA<sup>c</sup> University of Southern California Institute for Creative Technologies, 13274 Fiji Way, Marina del Rey, CA. 90292, USA<sup>d</sup> Emory University School of Medicine, 1256 Briarcliff Road, Atlanta, GA 30306, USA

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## ABSTRACT

Recent innovations in posttraumatic stress disorder (PTSD) research have identified new treatments with significant potential, as well as novel enhancements to empirically-validated treatments. This paper reviews emerging psychotherapeutic and pharmacologic interventions for the treatment of PTSD. It examines the evidence for a range of interventions, from social and family-based treatments to technological-based treatments. It describes recent findings regarding novel pharmacologic approaches including propranolol, ketamine, prazosin, and methylenedioxymethamphetamine. Special emphasis is given to the description of virtual reality and D-cycloserine as enhancements to prolonged exposure therapy.

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## 1. Introduction

While the diagnostic category of PTSD has existed only since 1980 when it was first included in the DSM III, hundreds of clinical trials have sought to identify methods of ameliorating its distressing symptoms. These methods have ranged from pharmacological approaches which directly treat PTSD and related symptoms to cognitive-behavioral treatments (CBT) that are based on principles of conditioning and learning. For example, exposure therapy, a CBT approach, is currently considered the first-line treatment for PTSD given its well-documented clinical efficacy (Foa, Davidson, & Frances, 1999; Foa, Rothbaum, & Furr, 2003). A recent Institute of Medicine (IOM) report concluded that exposure therapy is the only treatment with sufficient empirical evidence to recommend it (IOM, 2008). The efficacy of CBT trauma-focused treatments including prolonged exposure (Foa et al., 1999), cognitive processing therapy (CPT) (Monson et al., 2006) and eye movement desensitization and reprocessing (EMDR) (Bisson et al., 2007) have received support, while evidence for pharmacologic therapies remains inconclusive (IOM, 2008), although two medications have received an FDA indication for PTSD.

Despite the abundance of evidence pointing to the efficacy of exposure therapy, PTSD remains a difficult disorder to treat and identifying alternative treatment options is imperative. This is particularly true for Veterans and active duty personnel, given the likely return home of several hundred-thousand active duty soldiers over the course of the next 3 years combined with the probable need for re-deployment of U.S. soldiers to additional combat zones such as Afghanistan.

Although there have been significant advances in the treatment of PTSD, treatment failures persist. A meta-analysis of 26 studies with 44 treatment conditions reported that overall, 56% of those enrolled in treatment and 67% of those who completed treatment no longer met criteria for PTSD after treatment and 44% of enrollees and 54% of completers had clinically meaningful improvement by standards defined by the authors (Bradley, Greene, Russ, Dutra, & Westen, 2005). While these rates are impressive for short-term treatment of an often chronic disorder, the high rate of treatment failures calls for the innovation and dissemination of alternative or augmented treatments.

This article will review emerging psychotherapeutic and pharmacologic treatments for PTSD. While the term “emerging treatments” has no uniform definition in the literature, we use it to refer to interventions with some theoretical basis that have garnered the beginnings of scientific and popular support. By definition, this excludes interventions that have a strong scientific foundation or to which significant study has been dedicated such as prolonged exposure therapy (PE), CPT and EMDR which will not be addressed here. Our synthesis of the literature is presented below, with a description followed by a brief analysis of each treatment and with

special emphasis given to virtual reality (VR) exposure therapy and D-cycloserine as enhancements to traditional treatments as there is much excitement surrounding these approaches.

## 2. Psychological interventions

### 2.1. Social and family based treatments

#### 2.1.1. Couple and family therapy

PTSD has been associated with marital and relationship difficulty, aggression toward partners and children, sexual dysfunction and emotional distancing (Monson, Fredman, & Adair, 2008), with more than 75% of married or partnered Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) Veterans reporting problems with family relationships (Sayers, Farrow, Ross, & Oslin, 2009). Numerous couple and family treatment strategies have been developed but few have been studied. Riggs (2000) describes the two approaches to family treatment. The first focuses on the disruptions to the family system caused by the trauma and PTSD symptoms. Treatment targets reparations of the family dynamic and decrease of stress to the system, borrowing largely from couples and family treatments, and marginalizes treatment of the PTSD itself. The second focuses on the individual's PTSD and garners the support of the partner and/or family in helping the individual to recover.

Couples based treatments include Critical Action Theory for combat-related PTSD (Johnson, Feldman, & Lubin, 1995), emotionally-focused therapy (Johnson & Williams-Keeler, 1998) and others (Sherman, Zanotti, & Jones, 2005). However, no studies have evaluated the efficacy of these techniques. Erbes, Polusny, MacDermid and Compton (2008) propose the application of Integrative Behavioral Couple Therapy to the Veteran population, though no data supports its use as yet. The theoretical background highlights the role of experiential avoidance that causes the individual to distance him/herself from his/her interpersonal relationships and prevents the individual from approaching future opportunities to face discomfort, thereby hindering recovery.

In one of the more promising treatments with data on its efficacy, Monson et al. (2008) described Cognitive Behavioral Conjoint Therapy for PTSD, designed for couples where one or both partners have PTSD. The 15 session protocol treats the couple as a unit using three stages: 1) Psychoeducation and safety building, 2) Confronting avoidance, enhancing relationship satisfaction and improving communication, and 3) Cognitive interventions addressing relationship problems and symptoms of PTSD, focusing on maladaptive thoughts around the trauma. Only one preliminary uncontrolled study has been completed (Monson, Schnurr, Stevens, & Guthrie, 2004) with 7 married male Vietnam Veterans and their spouses. Significant improvement in PTSD scores by clinician rating and spouse rating were noted, though not by Veteran rating. Wives also reported marginally greater relationship satisfaction, while Veterans

reported improvements in depression and anxiety. A current NIMH funded grant is now devoted to the refinement and testing of this treatment.

Ford et al. (1998) studied the application of family systems therapy (FST) in 26 Operation Desert Storm Veterans who had been deployed to the European theater and requested family systems treatment as compared to a quasi-control group of 13 Veterans and their spouses who did not request treatment and 62 other Veterans from the same unit who were assessed 15–18 months after demobilization (posttest only group). The authors describe the treatment as focusing on the systemic effect of the stressors in one to five sessions lasting 90–120 min over a 2–8 week period. Goal setting and psychoeducation were followed by cognitive restructuring around “extreme beliefs” and strengthening feelings of trust, self-efficacy and safety. Structural systems interventions focused on restoring family roles, strategic prescriptions enhanced family members’ sense of control, and dysfunctional marital or parental patterns were identified and reworked. Finally, the Veteran was given the ability to share narratives of their most disturbing military experiences. Results indicated improvements in symptoms of anxiety and depression, as well as family systemic adjustment. The quasi-control group reported smaller improvement in psychiatric symptoms, and deterioration in family adjustment which may support the use of FST as a treatment. However, generalization from this study is poor due to significant variability in treatment time, design, and delivery, and the lack of randomization for group assignment.

Thus data on couples and family treatment is scarce, however the theoretical basis for its use in the treatment of PTSD is strong. The application to a military population is compelling: Returning Service Members often report feeling like they don’t belong or that they are misunderstood. Engaging the partner and the family is a natural area to intervene. It can increase feelings of acceptance and belongingness, help family members to understand the Veteran’s experience and illustrate to the Veteran that they have the support of their loved ones. The family relationship can serve as a support or obstacle in recovery from combat-related distress, underscoring the importance of the family relationship as a target for intervention (Erbes et al., 2008).

### 2.1.2. Interpersonal psychotherapy

The symptoms of PTSD are often accompanied by a disruption of social relationships from intimate familial connections to broader social and occupational networks. Interpersonal therapy focuses on social functioning which is theorized to consequently lead to improvements in all symptoms.

A pilot study of 14 subjects (Bleiberg & Markowitz, 2005) with chronic PTSD from diverse precipitating interpersonal traumas found that a 14 week, individual interpersonal treatment was successful in improving social relationships and in reducing symptoms of PTSD. The treatment focused on trust and interpersonal difficulties arising after the trauma and resulted in 69% of subjects showing a reduction of 50% in their CAPS scores and 12 of the 14 subjects no longer meeting criteria for PTSD after treatment.

Preliminary results of group applications of interpersonal therapy have been mixed. An 8 week interpersonal therapy group with 13 subjects with mixed adulthood precipitating traumas (including motor vehicle accidents, interpersonal violence and combat exposure) found interpersonal therapy to be effective in improving social functioning, symptoms of depression and general well-being, but only moderately effective in addressing symptoms of PTSD (Robertson, Rushton, Batrim, Moore, & Morris, 2007). Another study of interpersonal treatment in a group format randomly assigned 48 women with PTSD resulting from an interpersonal trauma to the treatment or waitlist control. Results showed that the treatment was significantly more effective in treating symptoms of PTSD and depression as compared to the waitlist group (Krupnick et al., 2008).

These mixed preliminary findings highlight the need for further research, including whether an emphasis on the social aspects of PTSD can effectively address PTSD symptoms such as reexperiencing and hyperarousal or whether interpersonal treatments are best used to augment traditional PTSD treatment.

## 2.2. Behavioral treatments

### 2.2.1. Behavioral activation

Behavioral activation (BA) entails a structured approach to increasing client engagement in activities, including identifying and scheduling events for homework. The technique may be especially relevant for individuals with PTSD where symptoms of avoidance and social isolation are prominent.

A case study of a police officer with a history of multiple trauma including military service treated with 11 sessions focusing on BA reported that the patient no longer met criteria for either PTSD or MDD following treatment. However, only significant reductions in the avoidance subscale emerged. (Mulick & Naugle, 2004).

A pilot study provided 11 Veterans with 16 sessions of BA utilized to identify avoided situations, plan goals, and practice activities. Therapists also worked with patients to identify triggers of anxiety and behavioral and emotional responses to it (Jackupcak et al., 2006). Between sessions, patients approached their avoided activities, although not those that were trauma specific. Of the 9 completers, CAPS scores showed a significant decrease pre- to post-treatment, but four of the five patients who showed a reliable change still met diagnosis of PTSD after treatment. There were no significant changes on mean depression scores.

A small randomized trial (Wagner, Zatzick, Ghesquiere, and Jurkovich, 2007) of 8 participants with traumatic injury compared 4 individuals receiving 4–6 sessions of BA to a TAU (treatment as usual) group 1 month after the traumatic injury occurred. Significant PTSD changes were noted in the BA group, but depression scores increased in half of the sample and decreased in the other half, which certainly needs clarification. Success in this small randomized trial may be attributable to the nature of a traumatically injured population in which concerns about physical limitations may increase behavioral avoidance and a treatment involving routine discussion with doctors regarding activity scheduling in light of the individual’s changed functioning can be especially significant.

These initial results do not seem to imply that the use of BA alone is sufficient to address the entire PTSD symptom picture. At present, BA is best treated as a component of other treatment approaches rather than stand alone treatment for PTSD.

### 2.2.2. Trauma Management Therapy

Trauma Management Therapy (TMT) was developed by Frueh, Turner, Beidel, Mirabella and Jones (1996) to address negative symptoms including social withdrawal, numbing, expression of anger, and interpersonal difficulties. The original protocol entailed 29 sessions over the course of 17 weeks. Psychoeducation and exposure were implemented in individual sessions. After the completion of exposure, programmed practice, entailing controlling one’s own exposure at home was implemented, and a social and emotional rehabilitation (SER) phase began. SER was conducted in small groups of 2–5 individuals and included social skills training and emphasized how to establish and maintain friendships. It included anger management and taught how to communicate to non-Veterans about military-specific issues. Results were very promising for the 11 completers (of 15) with significant improvement on anxiety, flashbacks, nightmares, sleep difficulty, heart rate reactivity and overall social functioning.

Initial results on TMT are promising, though length of treatment may be prohibitive in some contexts.

### 2.2.3. Interoceptive exposure

Interoceptive exposure, typically used in the treatment of panic disorder, entails inducing harmless physiological sensations that are often associated with arousal, for example, provoking shortness of breath through purposeful hyperventilation. The application to PTSD is a logical one, as the habituation to these physiological sensations and tolerance to distress may be helpful in addressing symptoms of anxiety, emotional and physical distress and hyperarousal.

A pilot study of 7 patients with diverse traumas incorporated interoceptive exposure (Wald & Taylor, 2007). Treatment consisted of 12 weekly 90-minute sessions, including 4 sessions of interoceptive exposure, 4 of imaginal exposure and 4 of in vivo exposure. Results at a post-treatment assessment showed improvements in PTSD symptomatology as well as anxiety sensitivity, posttraumatic cognitions, anxiety and depression in 5 of 7 patients. These gains were generally maintained at 1-month follow-up. At 3-month follow-up, 4 patients no longer met criteria for PTSD but 2 showed symptom intensification.

The limited data on this technique leaves many questions unanswered. This small study failed to show whether there is an additive effect to including this technique above the success of traditional treatment.

### 2.2.4. Mindfulness

Depersonalization is a state defined as a mechanical existence in which feelings are numbed and presence is surreal. This condition is diametrically opposed to the state of mindfulness in which one is in touch with the present moment with a full and vivid awareness of sensations and being. An assessment of 239 adults with trauma history without PTSD found that the Accepting without Judgment subscale of the Kentucky Inventory of Mindfulness Skills was significantly correlated with symptoms of PTSD, and the Acting with Awareness subscale was related to trauma-related reexperiencing symptoms (Vujanovic, Youngwirth, Johnson, & Zvolensky, 2009). It is logical, therefore to consider the use of mindfulness to enhance traditional treatments for trauma-related symptoms. The use of mindfulness has been incorporated into protocols for the treatment of PTSD (Bormann, Thorp, Wetherell, & Golshan, 2008; Wolfsdorf & Zlotnick, 2001) but studies have yet to evaluate its independent contributions.

### 2.2.5. Yoga and acupuncture

Scarce data supports the efficacy of yoga and acupuncture for PTSD, but studies are beginning to evaluate their use in this population. Unpublished data on the efficacy of yoga programs found some benefit for yoga in improving depression in a PTSD Veteran population, and an added benefit for some intrusive and hyperarousal symptoms with the addition of breathing techniques (Brown & Gerbarg, 2005). Positive results in the treatment of depression with yoga breathing show decreased levels of cortisol following treatment (Gangadhar, Janakiramaiah, Sudarshan, & Shety, 1999) and point to the need for further exploration of the effects of yoga and breathing techniques especially for the hyperarousal symptoms of PTSD.

One pilot study shows potentially promising results for the use of acupuncture in the treatment of PTSD (Hollifield, Sinclair-Lian, Warner, & Hammerschlag, 2007) in which 73 patients were randomly assigned to an acupuncture, group CBT, or waitlist condition. The acupuncture condition consisted of 2 one-hour sessions per week. Significant improvements were noted in the acupuncture group on PTSD, depression, anxiety and global impairment comparable to the group CBT condition and significantly different from the waitlist control group immediately following treatment and at a 3 month follow-up. Notably, group CBT is not yet a proven therapy for PTSD, and further research is necessary to evaluate the utility of this treatment.

## 2.3. Imagery-based treatments

### 2.3.1. Imagery Rescripting

Imagery Rescripting (IR) was introduced by Smucker, Dancu, Foa and Niederee (1995) as an enhancement to prolonged exposure for chronic sexual abuse survivors. It is conceptually based on an expanded information processing model with a key goal of therapy to facilitate cognitive change in the meaning of the events and the pathogenic schemas associated with it. The treatment is based on the theory that imagery has a more powerful impact on positive emotion than verbal processing, and therefore cognitive behavioral techniques used to promote positive change should also employ imagery (Holmes, Arntz, & Smucker, 2007). The patient first engages in an imaginal exposure which is immediately followed by a rescripting. During rescripting the patient is encouraged to imagine the trauma experience while developing mastery imagery by imagining themselves as an adult entering the room during the trauma and rescuing and protecting the vulnerable child. This phase lasts 4 sessions, with audiotapes of the entire exposure and rescripting for homework. For sessions 5 through 8, the imagery exercise begins with checking in with the child and focuses on the modification of pathogenic schemas.

A randomized trial (Arntz, Tiesema, & Kindt, 2007) assigned participants from an outpatient clinic with a variety of traumas to imaginal exposure with imagery rescripting (IE + IR) or imaginal exposure alone (IE). These patients were compared to a natural waitlist group necessitated when demand exceeded capacity of the clinic. Both treatment groups were treated with 10 sessions; 9 sessions contained imaginal exposure with or without rescripting; in vivo exposure was not utilized. No differences in post-treatment PTSD improvement were noted between the 2 treatment arms with treatment response at 63% for the IE group and 62% for the IE + IR group, but both groups fared better than those in the waitlist. Significantly greater anger control and reduction in guilt scores was reported in the IE + IR group with significantly fewer dropouts as compared to the IE group. No clinician administered measures were utilized.

In another study (Grunert, Weis, Smucker, & Christianson, 2007), 23 individuals injured in industrial accidents who still had PTSD following treatment with PE were treated with IR. PE was stopped when SUDS scores showed no habituation over time, though there is no information regarding how many sessions that averaged or what criteria were used to inform this decision. IR was then implemented, with each session containing imaginal exposure, mastery/adaptive imagery, and then post-imagery reprocessing. Following IR, significant improvements were noted in symptoms of PTSD, depression, and anxiety, although, again no clinician administered PTSD measures were utilized.

In sum, these studies indicate there may be utility in IR treatment for PTSD. Large-scale RCTs utilizing independent assessment comparing IE to IE + IR are needed indicate whether IR enhances imaginal exposure with improved treatment of negative symptoms and emotions such as guilt and anger. Proponents of IR claim it is more palatable than PE and point to the lower dropout rates in their study. They indicate that mastery and positive feelings elicited by the rescripted imagery is encouraging. However, these conclusions are premature and further research regarding engagement in the techniques is necessary.

### 2.3.2. Imagery Rehearsal Therapy

Imagery Rehearsal Therapy (IRT) was created by Krakow et al. (2000) to treat nightmares presenting in the aftermath of a trauma. IRT is delivered in a group format and has been administered in 1, 3 and 6 sessions that frame nightmares as trauma induced, habit-sustaining behaviors that may be controlled by the individual. Instruction in pleasant imagery is presented, and strategies for coping with unpleasant imagery are taught. In the next stage of treatment,



participants write down their nightmare and any changes to it they choose and then imagine the changed experience for 10–15 min, present it to the group, and rehearse the new dream daily.

One RCT conducted with survivors of sexual assault with PTSD ( $N = 168$ ) found that IRT showed moderate to large effect sizes compared to a wait-list control in nightmare improvement. PTSD symptoms significantly decreased in 65% of the treated sample, as compared to symptom exacerbation or no change in 69% of controls. Changes were maintained at 3 and 6 month post-treatment assessments (Krakow, Hollifield, Johnston, Koss, Schrader et al., 2001; Krakow et al., 2000). A study of crime victims with PTSD ( $N = 62$ ; Krakow, Johnston, Melendrez, Hollifield, Warner, et al., 2001) found similarly positive results which were maintained at 12 month follow-up. A study of adolescent girls with PTSD and a history of sexual abuse in a residential facility found that IRT improved frequency of nightmares, but did not affect overall sleep quality or PTSD symptoms compared to waitlist control (Krakow, Sandoval, Schrader, Keuhne, McBride et al., 2001). A study of “Sleep Dynamic Therapy”, a more comprehensive sleep treatment incorporating IRT, significantly improved sleep and PTSD symptoms in an uncontrolled study of 69 natural disaster victims (Krakow et al., 2002).

Applications to military populations have been mixed. A promising uncontrolled study of 12 male combat Veterans (Forbes et al., 2003; Forbes, Phelps, & McHugh, 2001) found positive results on outcome measures of nightmares, PTSD, depression and anxiety post-treatment and at 12 month follow-up. A study of 15 male Veterans with PTSD and trauma-related nightmares (Lu, Wagner, Van Male, Whitehead, & Boehnlein, 2009) attending 6 sessions of IRT did not find significant gains post-treatment on any outcome measure. However, at 3 months post-treatment, significant improvements were noted on trauma-related nightmare frequency and PTSD symptoms. None of these participants had been treated with PE or CPT and the authors posit that this treatment may not be ideal for Veteran populations or for individuals who are naïve about and hesitant toward trauma-focused therapy.

IRT has received support as an effective treatment for nightmares, but conclusions regarding improvements of other PTSD symptoms require more caution. Further study of effectiveness in military populations is especially warranted in light of the mixed but promising results among Veterans. A comparison of established treatments for PTSD with IRT could further elucidate the contribution of this technique.

#### 2.4. Therapies focusing on distress tolerance

##### 2.4.1. DBT

Dialectical Behavior Therapy (DBT) is a cognitive-behavioral treatment developed by Linehan (1993) for individuals diagnosed with borderline personality disorder (BPD). At the core of the treatment is an emphasis on emotion dysregulation. It also focuses on striking a balance between acceptance and change, with the use of validation as a principal technique in addressing this dialectic. DBT is often comprised of a combination of individual psychotherapy sessions and weekly skills building groups utilizing techniques such as mindfulness, emotion regulation, distress tolerance, and interpersonal effectiveness to address emotion regulation.

The application of DBT to individuals with PTSD has been proposed in two manners. The first entails the use of DBT for individuals with BPD with significant trauma histories and PTSD who have completed Stage 1 treatment targeting severe behavior dyscontrol but continue to experience emotion dysregulation. In Stage II DBT, individuals begin exposure to their trauma experience. No data has been accumulated studying this application (Welch & Rothbaum, 2007).

The second application of DBT entails the use of DBT techniques to prepare the patient prior to or concurrently with a traditional exposure protocol (Becker & Zayfert 2001). Several reasons are

offered for the applicability of this treatment to a PTSD population, including teaching the patient techniques to manage the strong emotions elicited by trauma-focused methods and the focus on emotion regulation with techniques to manage overwhelming emotion may make exposure treatment more palatable to hesitant clinicians.

Cloitre, Koenen, Cohen, and Han (2002) describe the use of these techniques in their “STAIR” program (skills training in affective and interpersonal regulation) in a population of patients with a history of CSA. Treatment consisted of two phases. Phase 1 consisted of 8 sessions focusing on psychoeducation, skills acquisition, application/practice and homework. Phase 2 entailed imaginal exposure, cognitive restructuring, a focus on coping with emotions post-exposure and emotion regulation. Comparisons with a group receiving 12 weekly phone contacts lasting 15 min each found greater improvements in the STAIR group on affect regulation, interpersonal problems and symptoms of PTSD following treatment and at 3 and 9 month follow-ups. Bradley and Follingstad (2003) similarly devoted 9 sessions to phase 1 treatment entailing psychoeducation about interpersonal victimization and affect regulation and breathing exercises. Phase 2 consisted of 9 sessions of structured writing about life experiences including traumatic victimization. Results showed significant improvement in PTSD symptomatology, mood symptoms and interpersonal problems compared to a control group.

The design of these studies makes it impossible to draw any conclusions regarding the effectiveness of DBT. As exposure techniques were utilized, treatment efficacy cannot be attributed to the enhanced protocols. Research must focus on what patient qualities suggest use of DBT, when it is most helpful to implement, and which skills in particular are useful.

##### 2.4.2. Acceptance and Commitment Therapy (ACT)

Advocates for the use of ACT for the treatment of PTSD conceptualize the disorder as a result of ineffectual control of unwanted thoughts, feelings and memories related to the trauma. ACT is utilized to reduce experiential avoidance (Orsillo & Batten, 2005) and help assimilate the experiences of the trauma memory into a valued life (Walser & Hayes, 2006). However, no empirical research has evaluated the use of ACT in the treatment of PTSD.

#### 2.5. “Power” therapies

##### 2.5.1. Thought Field Therapy

Thought Field Therapy (TFT), introduced by Callahan and Callahan (1997) is based on the foundation that control of all emotions and physiological activity is accessible in an individual through the energy points of acupuncture. TFT evokes changes in these mechanisms by activating meridian treatment points, in a process whereby clients imagine an anxiety-provoking situation, rate their distress and then tap on meridian points with their fingertips. No controlled studies have been published. Claims of success lack a scientific basis and rely on numerous “testimonials” for evidence. In sum, there is no convincing evidence for the theory or efficacy of TFT.

##### 2.5.2. Trauma Incident Reduction

Trauma Incident Reduction or TIR was introduced by Gerbode in 1985. The client is instructed to imagine the traumatic event without verbalizing it, followed by a verbal account. The process of TIR greatly approximates the work done in imaginal exposure, however, the authors assert that it is unique in its emphasis on client insight in the resolution process which distinguishes it from a conditioning model.

Only one controlled trial has been reported comparing TIR to a waitlist control in female inpatients with trauma history (Valentine & Smith, 2001), but participants did not have to have PTSD or any diagnosis for inclusion. Positive effects were noted after only one session, though it lasted 3–4 h long, compared to a waitlist control.

Other data consists only of uncontrolled case studies or case series (Figley & Carbonell, 1999; Carbonell & Figley, 1999).

It is unlikely that the reported success in the trial of TIR is due to anything unique in the treatment above and beyond the contribution of exposure to the trauma.

### 2.5.3. Visio Kinesthetic Disassociation

Visio Kinesthetic Disassociation, or VK/DD (Bandler & Grinder, 1979; Cameron-Bandler, 1978) uses “directed meta-self-visualization” to have clients dissociate and see themselves from the outside as they watch themselves in a traumatic scene. This dissociation helps to alter parts of the memory in order to correct negative emotions. Only one small baseline study (Hossack & Bentall, 1996) has been conducted with 5 patients, using 2 sessions of relaxation therapy followed by 2 session of VK/DD. Following this intervention, 3 of the patients showed significant reduction in frequency of intrusive imagery, 1 patient showed partial improvement and 1 showed no improvement. There exists only one other case series (Carbonell & Figley, 1999). The contribution of VK/DD to the PTSD treatment literature is unclear.

## 2.6. Technological-based treatments

### 2.6.1. Internet and computer based treatments

Internet based treatments have been proposed as a delivery-method for the treatment of anxiety disorders, especially PTSD that may address some logistical impediments including geographic and fiscal constraints. Specifically, it may offer treatment to those in remote areas who are limited in access to specialized healthcare by geography. It may also be appealing to individuals who are concerned with the stigma of mental health treatment and offer a viable alternative to individuals whose anxiety disorder precludes the travel or social interaction necessary in traditional treatments. A recent meta-analysis of Internet and computer-based treatments (ICT) of anxiety disorders (Reger & Gahm, 2009) found that among 4 waitlist controlled studies of PTSD, there was an overall moderate, significant weighted mean effect size of .75 across outcome measures. The authors conclude that although there is preliminary support for the use of ICT for PTSD, there is limited data to substantiate its use at this time.

Litz, Engel, Bryant and Papa (2007) assessed an 8 week cognitive behavioral Internet-delivered program “DE-STRESS” in a military population. Participants were randomly assigned to the DE-STRESS group ( $N=24$ ) or an Internet-based supportive counseling ( $N=21$ ). DE-STRESS entailed therapist-guided exploration of self-monitoring triggers, developing a hierarchy of trauma triggers, stress management, in vivo exposure, trauma writing sessions and relapse prevention. They had a dropout rate of 30% across treatment groups which is comparable to other studies of PTSD, with no differences between groups. The treatment group had significantly greater decreases in symptoms of PTSD, depression and anxiety 6 months following treatment.

Another model, interapy (Lange, Schrieken et al., 2000; Lange, Van de Ven et al., 2000; Lange et al., 2003) is a cognitive behavioral approach utilizing exposure and cognitive restructuring techniques. The treatment is conducted twice weekly for 5 weeks during which time the participant has 10 writing sessions lasting 45 min in which they describe their trauma in detail, work on cognitive reappraisal, and work on perspective of the effect of the trauma on their lives. To date, the largest assessment of Interapy was conducted in a community sample with 69 individuals in the treatment group and 32 waitlist controls (Lange et al., 2003). Participants in the treatment group improved significantly more than those in the waitlist control, with large effect sizes for PTSD symptoms and general psychopathology. Notably, many of the traumas endorsed in this population may not meet criterion A for PTSD (i.e. losing a loved one, divorce). Future

research should focus on the effectiveness of techniques delivered online and address questions such as whether more severe populations can be included in this type of treatment and issues related to ethical and legal considerations (Tate & Zabinski, 2004).

Videoconferencing involves the use of a camera to remotely project the image and sound of the individual onto a computer screen so the therapist and patient can interact by seeing and hearing each other in real time through a live connection. This has the benefits of addressing stigma and accessibility and allows therapists to monitor non-verbal behavior. A study of 32 individuals receiving CBT therapy in-person and 16 receiving treatment via videoconferencing found that after 16–25 weeks, significant improvement on PTSD symptomatology was noted in both treatment groups (Germain, Marchand, Bouchard, Drouin, & Guay, 2009). Importantly, no differences in effect were noted between groups, providing preliminary support for the use of videoconferencing in the treatment of PTSD.

### 2.6.2. Virtual reality: an emerging alternative treatment for PTSD

Special emphasis is given here to the description of virtual reality, as there is a substantive effort to implement its practice to treat U.S. military personnel deployed to Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF).

### 2.6.3. Rationale for Virtual Reality Exposure therapy (VRE)

Virtual reality (VR) integrates real time computer graphics and visual displays that allow users to feel a sense of immersion in the virtual environments. VR offers a promising technological adjunct to traditional imaginal exposure treatment of PTSD. Imaginal exposure requires patients to repeatedly narrate their trauma experiences with their eyes closed to facilitate engagement of their imaginative capacities. However, the avoidance inherent in PTSD may render engagement in imaginal exposure impossible for some patients. Moreover, most people with PTSD never seek treatment (Kessler, 2000). Some who do seek treatment are hesitant to engage in narrating the trauma repeatedly, and still others who express a willingness to undertake the exposure exercise are unable to engage their emotions or senses, retelling a flat emotionless tale that reflects their numbness and avoidance. These obstacles to engagement may lead to treatment failures, as theory suggests that emotional engagement and fear activation plays an essential role in exposure therapy. Foa and Kozak (1986) propose that fear relevant information associated with the patient’s memory for the traumatic event (i.e., the fear structure) must be accessed and activated through emotional engagement in order for a reduction in fear to occur. Repeated engagement with the fear structure in a safe therapeutic environment leads to a decrease in anxiety, through the processes of habituation and extinction, thereby allowing for the incorporation of new information. Furthermore, research has established that poorer emotional engagement in treatment predicts poorer treatment outcome (Jaycox, Foa, & Morral, 1998).

VR theory proposes that these obstacles may be addressed by directly delivering multiple sensory cues that may evoke the trauma memory. Patient’s imaginative capacities are augmented with visual, auditory, olfactory, and even haptic computer-generated simulation experiences, increasing the patient’s “sense of presence” in the virtual environment. VR exposure may also attenuate dropouts associated with avoidance by offering a graded and systematic approach to the avoided stimuli that can be carefully monitored and tailored to the individual patient’s needs (Hodges, Anderson, Burdea, Hoffman, & Rothbaum, 2001).

### 2.6.4. Application of VR to treat anxiety disorders

The application of VR to treat psychiatric disorders began in the 1990s with an emphasis on anxiety disorders, though VR has been used to treat diverse disorders, including addictions, autism-spectrum disorders, as well as motor and cognitive assessment and

rehabilitation (Glanz, Rizzo, & Graap, 2003; Rose, Brooks, & Rizzo, 2005; Rizzo & Kim, 2005; Rothbaum, 2009). Two recent meta-analyses (Parsons & Rizzo, 2008; Powers & Emmelkamp, 2008) of VR studies for anxiety disorders found that VRE represents an effective treatment modality for various anxiety disorders, including fear of flying, social phobia, and specific phobias, with effect sizes ranging from .92 to 1.79, and with an average overall effect size across studies of .96 (Parsons & Rizzo, 2008).

Rothbaum et al. (1995a,b) were the first to validate the efficacy of VRE with a psychiatric population (fear of heights) and found that VRE was effective in significantly reducing fear of and improving attitudes toward heights, in contrast to a control group that reported no such changes. Since then, multiple case studies and open clinical trials have successfully applied VR to treat phobias.

The first VR application for PTSD, known as Virtual Vietnam, was developed by researchers at Emory University and Georgia Institute of Technology in 1997 to treat PTSD in Vietnam Veterans. In a case study, the first Vietnam Veteran to be treated was a 50-year-old Caucasian male still experiencing PTSD 20 years following the Vietnam War. The results of this trial found that he experienced improvement on all measures of PTSD as well as maintenance of these gains 6 months later (Rothbaum et al., 1999). Following this case study, an open clinical trial of 16 male Vietnam Veterans with PTSD, consisting of an average of 13 VRE sessions, also found significant reductions in PTSD and related symptoms (Rothbaum, Hodges, Ready, Graap, & Alarcon, 2001). At 6 month follow up, a reduction in PTSD symptoms was found, including statistically significant reduction from baseline in symptoms associated with specific reported trauma experiences on the primary outcome measure, the Clinician Administered PTSD Scale (CAPS). Eight of 8 participants at the 6-month follow-up reported reductions in PTSD symptoms, ranging from 15% to 67%. Rothbaum et al. (2001) reported several key findings about the utility of VRE. Out of the 16 participants treated with VRE: 1) no person decompensated as a result of the study, and 2) no participant was hospitalized during the study for complications related to VRE.

In 2002, Difede and Hoffman (2002) published a case study applying VRE to treat PTSD consequent to the World Trade Center attacks of September 11, 2001. The virtual environment stimuli included actual 9/11 audio recordings made by national news networks, planes flying into the two towers, explosions and falling debris as seen from the WTC, as well as human avatars falling from the burning WTC towers. The first case report applied VRE over six one-hour sessions, with reductions in depression symptoms, as measured by the Beck Depression Inventory, and reductions in PTSD symptoms, as measured by the CAPS, by 83% and 90%, respectively. This case underscores some of the possible added value of VR, given that the individual previously failed to improve with traditional exposure therapy. In a follow up clinical trial, participants representing a range of those with direct exposure to the attacks including firefighters, disaster rescue and recovery workers, and civilians, were assigned either to VRE ( $n = 13$ ) or a waitlist (WL) control group ( $n = 8$ ) (Difede et al., 2007). In contrast to the WL group who did not evidence any reduction in PTSD symptoms, the group receiving VRE demonstrated a significant decrease in CAPS scores both relative to pre-treatment and to the WL group with a between-groups post treatment effect size of 1.54 which were maintained at six-month follow-up. Interestingly, five of the participants in the VRE were nonresponders to prior imaginal exposure.

Researchers worldwide are actively evaluating virtual environments to treat PTSD. Beck, Palyo, Winer, Schwagler and Ang (2007) utilized driving scenarios to treat PTSD resulting from motor vehicle accidents (MVAs). An uncontrolled trial of six subjects found that 10 sessions of VRE was successful in treating symptoms of PTSD, with patients reporting high levels of presence and satisfaction with treatment. Saraiva et al. (2007) presented a case study of an MVA survivor treated with VRE for 4 sessions, with resulting reductions in

both psychophysiological activity and PTSD symptoms, although criteria was still met for severe PTSD. Finally, Josman et al. (2006) describe a virtual bus environment that simulates a terrorist attack to treat survivors of terrorist bus bombings in Israel.

#### 2.6.5. Application of VR for PTSD among OIF/OEF soldiers

The need to develop alternative treatments, especially ones that may appeal to the younger population of returning OIF/OEF military is underscored by the findings of Hoge et al. (2004). They report that among Iraq/Afghanistan War Veterans who endorsed symptoms indicative of a disorder, only 23 to 40% sought mental health services, especially citing concerns about stigmatization. VR may represent a palatable variation on the traditional approaches to treatment, could be promoted in a way that reduces the typical stigma associated with seeking mental health treatment, and, given its emphasis on technology, could be couched as a “high-tech” tool that helps soldiers with “post-combat reintegration training,” especially given that the current generation of active duty personnel have grown up with gaming technology (Rizzo, 2009). The Office of Naval Research commissioned two open trials designed to evaluate the efficacy of VR in treating PTSD in OIF/OEF active duty soldiers.

#### 2.6.6. Virtual Iraq

Virtual Iraq consists of two primary virtual scenarios, a Middle Eastern city and a Humvee scenario that allows the user to drive down a desert road. Two additional environments (i.e., a USA and an Afghanistan-specific environment) have recently been added.

The flexibility of the Virtual Iraq system enables the therapist to manipulate the environments in multiple ways in real time, including the establishment of ambient settings (e.g., time of day, weather conditions, background noise, night vision options), and the introduction or removal of animated vehicles, pedestrians (civilian and military), and helicopters/jets taking off, flying overhead, or landing. It also provides options for the delivery of a variety of combat relevant elements, such as improvised explosive devices (IEDs), rocket-propelled grenades (RPGs), car bombs, and insurgent attacks, all of which can be actuated via mouse-clicks on a clinician control panel.

The city scene allows the user to walk around an 18-square-block Middle Eastern city, with either a gamepad controller, or with a “thumbmouse” mounted on a realistically weighted replica of a M4 rifle. The city includes a variety of scenes such as a marketplace, warehouses, a security checkpoint, mosques, empty streets, apartments, old buildings, and dirt lots with piled garbage. The functionality of this environment allows for the patient to both enter buildings and climb stairs to get to rooftops, with various audio-visual events such as explosions, helicopters flying, gunfire, and people walking. The Humvee scenario incorporates an expansive sand dune or mountain backdrop interspersed with palm trees and other vegetation, intact and broken down structures, bridges, battle wreckage, a checkpoint, debris and virtual human figures who create ambushes at various points, all controlled by the therapist. Patients can be positioned as the driver, passenger, or in the turret, alone, or with a team inside the Humvee, as well as with or without a convoy of other Humvees. A standard gamepad controller is used to drive the vehicle, and features vibrotactile sensations that the user can feel when explosions occur.

In both environments, the visual stimuli presented via the head mounted display (HMD) can be supplemented by directional 3D audio, vibrotactile, and olfactory stimuli. Customized, coordinated vibratory sensations (e.g., explosions, vehicle engine rumble) are provided by inexpensive audio-tactile sound transducers placed in a low-cost floor platform beneath the patient. Olfactory cues are also possible via a USB-enabled device that uses up to 8 scent cartridges, a series of fans, and a small air compressor to deliver scents (e.g., burning rubber, cordite, garbage, diesel fuel, Middle Eastern spices, gunpowder) to participants with the click of a mouse. The therapist



controls each stimulus via mouse interaction with a control panel on a computer screen while in full audio contact with the patient. This enables a clinician to match or supplement the patient's spoken trauma narrative within the VR simulation and allows for a customized approach that is individually tailored to the patient's experience and treatment progress.

In initial VRE clinical trials using the Virtual Iraq, the standard treatment protocol consisted of one to two weekly, 90–120 minute sessions, over 5 to 10 weeks. The VRE exposure exercises followed the principles of graded behavioral exposure and the pace was individualized and patient-driven. Assessment data was obtained at baseline and prior to sessions 3,5,7,9, and 10, as well as at one week and three months posttreatment.

Results from a case study from Emory University reported a 56% reduction in CAPS scores following VRE for an active duty OIF soldier (Gerardi, Rothbaum, Ressler, Heekin, & Rizzo, 2008). In another case study, six sessions of VRE were effective in reducing PTSD and psychological distress in an active duty army soldier (Reger & Gahm, 2008). An open clinical trial using VRE for PTSD with active duty personnel yielded promising results with 20 study participants completing treatment at two sites, Naval Medical Center San Diego and Camp Pendleton (Mclay et al., under review; Rizzo et al., 2009; Yeh et al., 2009). For this sample, (19 male, 1 female, mean age = 28.1) scores on the PCL-M scores decreased from a mean of 54.5 to a mean of 35.6. Correcting for the PCL-M no-symptom baseline of 17 indicated a 50% decrease in symptoms and 16 of the 20 completers no longer met DSM criteria for PTSD at posttreatment. Scores on measures of anxiety also significantly decreased by 33% and depression scores significantly decreased by nearly 50%. The average number of sessions for this sample was just under 11. Notably, two of the successful treatment completers had documented mild and moderate traumatic brain injuries, which suggests that this form of exposure can be useful for this population. Currently, Virtual Iraq is being implemented clinically and in clinical research trials by applying VRE to treat PTSD among Veteran and active duty OIF/OEF Service Members at numerous army medical centers, universities, over 15 Veterans Administration Hospital sites, and 8 U.S. Air Force bases around the country.

#### 2.6.7. Virtual Reality Graded Exposure Therapy (VRGET)

A second open trial is underway assessing the effects of Virtual Reality Graded Exposure Therapy (VRGET) among OIF/OEF active-duty personnel. VRGET applies graded exposure while presenting VR-based visual and auditory stimuli (e.g., combat scenarios and sounds, other common household sounds, people talking). A case study described the treatment of a 32 year-old male, Second Class Petty Officer and Corpsman (Wood et al., 2007). VRGET consisted of 10 90-minute weekly sessions, including presentation of meditation and attentional refocusing and applying these skills while relating a narrative of the trauma. The authors reported that on the PCL-M, the level of "intrusive PTSD symptoms" suggested the presence of clinical PTSD at both the pre- and mid-treatment assessments, while PCL-M scores were lower at the post-treatment assessment. However, there is not sufficient information provided to characterize whether these changes were significant. The authors comment that they decided to continue VRGET with this individual for an additional 10 sessions for a total of 20 sessions.

This was followed by a case series of six active-duty corpsmen with a mean pre-treatment PCL-M score of 47.3 (Wood et al., 2008). Following the treatment of VRGET combined with meditation and attentional refocus, "partial remission" was reported in four of the six subjects, though statistical information was not provided. Clinical trials are necessary to determine the value of VRGET, as these case studies offer limited information from which to draw conclusions.

The use of virtual reality seems especially promising as an emerging treatment for PTSD with special relevance to military

populations. Challenges to the utility of virtual reality include the expense of the systems and the need to create new environments for each traumatic event. Yet with the progression of the field, these challenges are becoming easier to address. Price of equipment in the past ten years has decreased dramatically and further deflation is anticipated. Current environments are often developed with key elements that can be used as a framework in the creation of other settings addressing other different types of traumas, and one flexible environment such as that of Virtual Iraq can incorporate the trauma of thousands who were exposed to events in similar contexts. Nevertheless these challenges are notable, and the key question remains whether VRET offers efficacy beyond the rates of treatments utilizing prolonged exposure.

### 3. Pharmacologic treatments

Though recent guidelines suggest that psychotherapy should be initiated as a first-line treatment for PTSD before pharmacological options (National Collaborating Centre for Mental Health, 2005), medications are often necessary to palliate symptoms, and the pursuit of more effective medication is essential to developing a range of effective treatment options. The most commonly used medications have been antidepressants, and specifically SSRIs (Davidson, 2000; Davidson & Connor, 1999). Stein, Ipser, and Seedat (2006) reported in a Cochrane systematic review that pharmacologic intervention can be effective, especially with the use of SSRIs. However, the difference between medication and placebo in short-term intervention was 5.76 points on the CAPS and the NICE guideline (2005) reported that with few exceptions, the overall effect size in medication trials did not exceed the criterion of 0.5 required to be clinically effective. The Cochrane review (2006) reported that war Veterans were more resistant to medication than other groups, though more research is required to ascertain the precise nature of this relationship.

#### 3.1. D-cycloserine

Among pharmacologic innovations, arguably the most significant in its potential is D-cycloserine (DCS; trade name Seromycin), which is being used in conjunction with prolonged exposure treatment. DCS is a broad-spectrum antibiotic that has been used in clinical trials over the last decade as a cognitive enhancer. It is a partial agonist at the N-methyl-D-aspartate (NMDA) receptor, which is known to play an essential role in learning and memory. Both fear learning and extinction are blocked by antagonists at the glutamatergic NMDA receptor, and DCS has been shown to facilitate extinction learning in animal models of conditioned fear and in some human trials of other types of learning (Davis, Barad, Otto, & Southwick, 2006; Davis, Ressler, Rothbaum, & Richardson, 2006; Ledgerwood, Richardson, & Cranney, 2005; Walker, Ressler, Lu, & Davis, 2002).

In the first clinical study of DCS (Ressler et al., 2004), a double-blinded randomized controlled clinical trial was conducted with 27 patients with acrophobia. Patients were assigned to receive either DCS or placebo prior to 2 sessions (a suboptimal dose) of VR exposure therapy. At assessments 1–2 weeks and 3 months following the exposure, patients in the DCS group reported significantly less anxiety and had lower skin conductance fluctuations in the virtual environment compared to those in the placebo group. In addition, at 3 months post-treatment, those with DCS reported greater real-life exposure to heights and had greater impressions of self-improvement relative to those in the placebo group.

Positive results were reported from a double-blind randomized controlled trial of DCS conducted with 27 individuals with social phobia in a 5-session treatment (Hofmann et al., 2006). Patients who took DCS prior to the 4 sessions of exposure to social situations showed significantly greater reductions in general social anxiety symptoms, both immediately post-treatment and at a one-month



follow-up, compared to individuals in the placebo condition. Similarly positive results were found in a randomized controlled trial of 56 participants with social anxiety (Guastella et al., 2008). Those who received 50 mg of DCS prior to treatment showed significantly greater improvement on symptom severity, dysfunctional cognitions, and life-impairment as compared to a placebo group.

Several studies are currently evaluating the use of DCS to enhance imaginal exposure or VR enhanced exposure for the treatment of PTSD. The mechanism by which DCS operates can be conceptualized using the same principles as those used for other anxiety disorders. The repeated exposure to the traumatic memory utilized for PTSD treatment facilitates extinction of feared emotional responses to the memory. Facilitation of this fear extinction by an agonist at the NMDA receptor may enhance or accelerate treatment effects of exposure for PTSD.

In sum, research indicates that DCS may facilitate extinction of fear, lead to generalized extinction and reduce post-treatment relapse after another event (Davis, Ressler et al., 2006). This seems a promising medication with low dosage and frequency of intake which may enhance efficiency of treatment. However, data has not yet emerged in PTSD populations and there is a clear need for further study of DCS.

### 3.2. Propranolol

Propranolol is a non-selective beta-adrenergic blocker used in the treatment of hypertension. Prolonged adrenergic activation in the immediate aftermath of a trauma has been linked to increased risk for PTSD (Vaiva et al., 2003), possibly through increased fear conditioning (Orr et al., 2000). Pitman et al. (2002) posit that this is a consequence of a release of an excessive amount of epinephrine during the trauma, and that the administration of propranolol soon after a trauma could cause the blockage of the receptors and consequently prevent the development of PTSD. Preliminary research on the use of propranolol as a preventative measure against PTSD supports this theory (Pitman et al., 2002; Vaiva et al., 2003).

These principles were recently applied to a treatment model in a randomized controlled study of 19 patients with chronic PTSD (Brunet et al., 2008). Individuals with PTSD wrote a script of their trauma experience and then received propranolol or a placebo. One week later psychophysiological reactivity was measured while participants listened to a recording of a script of their trauma experience. Individuals who received propranolol at the initial session had significantly lower levels of reactivity compared to the placebo group, perhaps due to drug inhibition of memory consolidation. Notably, PTSD symptoms were not included as an outcome measure in this study. The applications of these findings to PTSD treatment cannot be determined until further studies have been performed.

### 3.3. Ketamine

Ketamine is a nonbarbiturate anesthetic administered intravenously especially to burn patients in some military hospitals. Ketamine is associated with dissociation and psychosis, leading to the concern that it will yield greater rates of PTSD. One retrospective study of 50 victims of moderate accidental trauma compared those who received ketamine ( $n=13$ ) to those who received opioids ( $n=24$ ) or non-opioid analgesics ( $n=13$ ) in their initial emergency treatment (Schonenberg, Reichwald, Domes, Badke, & Hautzinger, 2008). Assessments occurred within three days of admission and found increased symptoms of acute stress disorder (including symptoms of dissociation, reexperiencing, avoidance and hyperarousal) in the ketamine group relative to the other two groups.

McGhee, Maani, Garza, Gaylord and Black (2008) found vastly different results in a retrospective chart review of 147 injured OIF/OEF patients at one military medical center, comparing 119 patients who

received ketamine during their hospitalization to 28 who did not, although amount of time between injury and PTSD assessment is unclear. Contrary to expectation, those who received ketamine had significantly lower rates of PTSD than those who did not (26.9% vs. 46.4%, respectively), despite more severe burns, greater burn size, longer stay in the intensive care unit and more surgeries. Ketamine acts as an antagonist at the NMDA receptor which may cause a disruption of the memory process, either of the hospital experience or the traumatic experience itself. The authors warn, however, that these results must be interpreted with caution since the negative correlation between PTSD and ketamine, while present, was weak (ROC curve = 0.569). Furthermore, patients were not randomized in this retrospective review, and it is unknown what factors influenced whether the patient received ketamine. Thus, further research must explore the nature of this relationship and rule out the possibility of other factors driving this correlation between ketamine and lower rates of PTSD.

### 3.4. Prazosin

Increased central nervous system adrenergic activity, resulting in greater release of norepinephrine and increased sensitivity to norepinephrine at receptor sites, has been implicated in PTSD (Taylor, Freeman, & Cates, 2008). Increased activity occurs especially at night and has been associated with poor sleep and nightmares. Prazosin, an alpha-1 adrenergic receptor blocker, is primarily prescribed as an anti-hypertensive and for the treatment of benign prostatic hyperplasia (Miller, 2008). Its role in inhibiting adrenergic activity suggests it may be a useful tool in targeting these PTSD symptoms.

Case studies, retrospective chart reviews, and open label trials have all reported the effectiveness of Prazosin for the treatment of nightmares (Taylor, Martin et al., 2008). An initial randomized crossover trial (Raskind et al., 2003) assigned 10 Vietnam Veterans with PTSD for more than 25 years to a prazosin or placebo group. Each group received treatment for 9 weeks, then after a 2-week medication-free period were given the other treatment. CAPS scores and number of distressing nightmares at 20 weeks significantly differed between prazosin and placebo groups ( $p < .001$ ). A larger randomized controlled trial (Raskind et al., 2007), randomly assigned 40 Veterans with nightmares and sleep difficulty to receive Prazosin or placebo prior to bedtime. Medication dosage began at 1 mg but was increased over the course of treatment if symptoms were not responding, with a maximum dose of 15. Four Mean dosage of prazosin was 13 mg ( $SD=3$ ). After 8 weeks, significant differences emerged between groups on number of distressing nightmares, and sleep quality. Individuals in the prazosin group reported a mean 50% decrease in nightmares as compared to a 15% decrease for the placebo group ( $p = .02$ ). A recent study of 22 Veterans with PTSD found prazosin was effective not only in treating nightmares but also non-nightmare distressed awakenings (Thompson, Taylor, McFall, Barnes, & Raskind, 2008).

This evidence suggest that prazosin may be a promising adjunctive medication to target specific sleep-related disturbances in PTSD patients, but RCTs must be conducted to answer questions regarding best dosage, effectiveness for women and non-military populations and actual clinical significance. Trials are ongoing in civilian populations.

### 3.5. Methylendioxyamphetamine (MDMA; Ecstasy)

The clinical use of MDMA to enhance psychotherapy was documented as early as 1978, though its prohibition as an illegal substance in the mid 1980s precluded early clinical research to explore its efficacy (Parrott, 2007). More than a decade later, the Food and Drug Administration approved the clinical trial of MDMA for enhancing psychotherapy for chronic PTSD (Doblin, 2002). Though

conclusive results have yet to be published, a recent review by Parrott (2007) outlines the theory behind the use of MDMA. The first of three models that he cites for the use of MDMA assisted-therapy proposes that during the session, negative material related to fearful memories (i.e., a trauma) may emerge and can then be processed with a therapist without intensely negative emotions. The second model focuses on the positive moods induced by MDMA that lead to the therapeutic goals of feelings of wholeness and integration. The final model emphasizes the improved trust and emotional alliance that is formed between the patient and the therapist as a result of the MDMA, which may be a key ingredient in the success of treatment.

Parrott described the beneficial effects of MDMA as reported in the existing literature as including recognition of positive aspects of self and others; positive moods, cognitions and beliefs; the emergence of past negative events and the decrease in negative feelings associated with it; and the strengthening of the therapeutic alliance. However, he also cautions that reported negative effects must be further explored. These include negative mood states and psychobiological reactivity that have been reportedly associated with MDMA, negative emotions and psychobiological distress that have been noted in the aftermath, and the question of the use of CNS stimulants in a vulnerable psychiatric population which may potentially lead to a worsening of symptoms. Thus, there is a significant need for further research regarding both the positive and negative effects of MDMA before it may be considered for clinical use.

#### 4. Conclusions

The recent proliferation in treatments for PTSD suggests that researchers are beginning to address the need to develop and evaluate alternatives to the current armamentarium. While there are myriad treatments emerging, few, if any, have sufficient evidence to draw conclusions about their efficacy. However, technological based treatments have the strongest preliminary evidence. The possibility inherent in Internet and teleconferencing based interventions is especially important given the logistical impediments to care for those who live in remote areas. Another technologically-based treatment, VR enhanced exposure therapy seems a promising intervention, especially for military populations, with convergent evidence amassing across multiple trauma populations and anxiety disorders. Currently ongoing RCT's comparing VR to imaginal exposure will determine its place in the PTSD treatment arsenal. Further research should also focus on creating turnkey applications that are easy to use and more easily configured to individual traumas.

With regard to pharmacologic treatments, D-cycloserine offers exciting possibilities for enhancement of exposure, with preliminary data from other anxiety disorders suggesting that it may significantly reduce time in treatment. Though data for the treatment of PTSD is still in the preliminary stages, if similar results are shown with PTSD patients, it could have a significant impact on treatment compliance, cost of treatment, and disability by reducing the time in treatment. It remains to be seen whether conclusive evidence regarding the utility of propranolol, ketamine and MDMA will be forthcoming. However, prazosin has been shown to be effective in the treatment of nightmares related to PTSD. This is an exciting development as sleep difficulties remain one of the most difficult PTSD symptoms to treat.

Some emerging approaches offer promising new conceptualizations of treatment based either on theoretical considerations or empirical evidence regarding the phenomenology of PTSD, but lack the data that would allow a conclusive evaluation of their merits. Given the insidious interpersonal effects of PTSD, social and family based treatments are conceptually compelling. As couples, family, and interpersonal therapies have support from preliminary studies and a sound theoretical and empirical foundation, further research in this

area is likely to yield important treatment advances and should be a priority.

Therapies aimed at augmenting exposure therapy by increasing distress tolerance and compliance or targeting negative symptoms and sleep difficulties are significant in their attempts to address "treatment failures." Behavioral treatments such as behavioral activation and mindfulness may be effective to enhance protocols with proven techniques shown to ameliorate some but not all PTSD symptoms, but not as a stand-alone treatment for PTSD. Trauma management therapy shows promise for the treatment of negative symptoms of PTSD in conjunction with exposure therapy. Imagery-based treatments show potential; IRT is effective in the treatment of nightmares in PTSD but has questionable effect for other symptoms. IR emerges as an effective treatment for PTSD, though no data exists to compare its efficacy to that of imaginal exposure. No conclusions can be drawn about treatment aiming to affect emotion around exposure, as use of ACT in PTSD populations has not yet been documented, and DBT shows promise in women with a history of childhood abuse, but generalizability is unclear. "Power" therapies lack any evidence to back their lofty claims of success.

Caution should be taken before employing any emerging therapies outside of research protocols developed to test their efficacy. In community care and private practice, empirically-validated treatments recommended by the PTSD Expert Consensus Guidelines should be used as first-line treatments with emerging therapies utilized as alternatives only when the first line treatment is not successful or requires augmentation. Randomized controlled trials are necessary to further evaluate the contribution of these alternative and augmented treatments, but the future clearly holds exciting possibilities for the treatment of PTSD.

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