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PTSD AND MEDICATION

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The main treatments for post-traumatic stress disorder (PTSD) are psychological therapies and medication. On the medication side, empirical evidence is strongest for the selective serotonin reuptake inhibitors (SSRIs) sertraline, paroxetine, and fluoxetine and the selective serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine. But particularly in the treatment of PTSD it is important that the treatment is comprehensive, including psychotherapy and other therapies, and takes into account the individual characteristics of the patient when selecting the different treatment modalities and the timing of when to use them.

It is quite clear from the available study data and clinical experience that medication can offer some support in the treatment of PTSD, but that psychotherapy should always be considered the first-line treatment and medication as a valuable and potentially quite helpful add-on. Unfortunately, mental compartmentalization in the choice of effective treatment constellations in clinical practice and research often hinders the formulation of the most effective treatment plan. Few studies have, for example explored, how best to combine a particular psychotherapy with a specific type of medication. But that would be desperately needed.

Keywords: post-traumatic stress disorder, PTSD, medication, pharmacology, treatment, psychiatry

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Introduction

Post-traumatic stress disorder (PTSD) is a mental disorder that can develop after a person is exposed to a traumatic event, such as sexual assault, warfare, traffic collisions, child abuse, or other threats on a person's life. Symptoms may include disturbing thoughts, feelings, or dreams related to the events, mental or physical distress to trauma-related cues, attempts to avoid trauma-related cues, alterations in how a person thinks and feels, and an increase in the fight-or-flight response. About ten percent of people experiencing a traumatic event will subsequently develop post-traumatic stress disorder (PTSD). (Koch et al., 2014) PTSD is characterized by an exaggerated fear response which fails to extinguish over time and cannot be inhibited in safe contexts.

The Interpersonal Aspect

People who experience interpersonal trauma such as rape or child abuse are more likely to develop PTSD as compared to people who experience non-assault based trauma, such as accidents and natural disasters. (Zoladz & Diamond, 2013) About half of people develop PTSD following rape. From this we can already see the importance the interpersonal dimension, and hence communication plays in the development of trauma, which is also the focus of Communication-Focused Therapy®® (CFT) as developed by the author. (Haverkampf, 2020)

The Effect of PTSD on Health Outcomes

PTSD symptoms seem to mediate the effects of traumatic injury on health outcomes. Cody and Beck examined cross-sectional relationships between injury, PTSD, and pain and psychiatric medication use in 2 trauma-exposed samples, female survivors of motor vehicle accidents and intimate partner violence. The analysis of the data suggested that PTSD symptoms mediate the relationship between injury severity and use of pain medications and psychiatric medications. Mediation, however, was not moderated by trauma type. (Cody & Beck, 2014)

Socioeconomic Costs

The total direct and indirect cost of PTSD in Northern Ireland in 2008 has been estimated at £172,756,062, which is still likely to be conservative due to the exclusion of a number of cost categories (Ferry et al., 2015) It is clear that the treatment of trauma can benefit the individual and society as a whole tremendously. Unfortunately, often the focus is either only on medication or on psychotherapy, and while psychotherapy is the preferred long-term strategy, the question about the need for medication should have a place in an integrated treatment plan.

Medication

A few available drugs provide some benefit in the management of PTSD symptoms and have been approved by the US Food and Drug Administration (FDA) for the treatment of PTSD, but most meta-analytic reviews have concluded that effect sizes are small and there may be relatively little benefit for combat veterans, PTSD patients with early life-trauma or patients with complex PTSD. Popular augmentation strategies using second-generation antipsychotic medication were also recently shown to be ineffective in PTSD. (Neumeister, 2013)

There is an urgent need to address a critical lack of advancement in the psychopharmacologic treatment of posttraumatic stress disorder (PTSD). The clinical, social, and financial burden of ineffectively treated PTSD is enormous. The impact of PTSD morbidity and mortality is further magnified by its substantial disruptions in family, workplace, and societal contexts. (Krystal et al., 2017)

The prevalence of PTSD in the general population for lifetime is approximately 8% and just under 4% for the current year, making it the fifth most prevalent mental disorder in the United States. (Krystal et al., 2017) In recent years, numerous lines of converging evidence have revealed an association between post-traumatic stress disorder (PTSD) and impaired physical health outcomes, including cardiovascular disease and metabolic syndrome.

Self-Care and Compliance

Trauma shatters the safety and sense of self one experiences, which also effects how people care for themselves. In a study by Zen and colleagues, PTSD was associated with significantly higher rates of physical inactivity in terms of overall exercise, light exercise, and self-rated level of exercise. People with PTSD were also more likely to report medication nonadherence, including forgetting medications or skipping medications. (Zen, Whooley, Zhao, & Cohen, 2012) The investigators found that depression (and lower income) seemed to explain a large part of these associations.

Emotions

Medication can be emotionally flattening (Haverkampf, 2013), which can cause problems in the treatment of PTSD, particularly in psychotherapy. Wang and colleagues revealed in their study a high level of persistent anger and hatred in patients with PTSD who had been injured in combat. (Wang et al., 2012) The medication should support therapy rather than stand in its way, and this requires attention to all aspects of PTSD, including the emotions. Since the emotions are processed information, one needs to have a keen eye on how the trauma has affected the processing of information and

meaning in the particular patient, not only when considering therapy but also when thinking about medication.

Central clinical features of PTSD are the persistence of a heightened salience of traumatic memories and a failure of the extinction process to diminish the impact of traumatic memories. In PTSD, hyper consolidation of emotionally aversive memories is likely the initiating event following exposure to trauma that results in pathology. (Neumeister, 2013)

The Self

As already described by the author elsewhere, the sense of self is the experience of information flows within oneself, and a reduced ability to discern and work with them can lead to a fragmentation of the self (Haverkampf, 2017c, 2017d). Neurobiologically, there are several centers in the brain that have been singled out in the past for the role they play in the experience of the self, although it is central to acknowledge that the brain as a whole with its myriads of information pathways and ability to integrate information gives rise to the sense of self, as well as more specific and technical attributes, such as personality characteristics.

The parietal cortex supports the 'first person perspective' on the visual world, unconsciously framing the visual object stream. Some prefrontal areas select and interpret conscious events for executive control. Such functions can be viewed as properties of the subject, rather than the object, of experience – the 'observing self' that appears to be needed to maintain the conscious state. While humans seem to have a common intuition of an observing self that has access to conscious sensations, inner speech, images and thoughts, it is important to note that the self as described above is even more fundamental, as it is not derived from specific information, but the experience of the flow itself.

Medication

The largest body of evidence for short- and long-term efficacy of medication currently exists for SSRIs, with some support for the selective noradrenergic reuptake inhibitor venlafaxine and the atypical antipsychotic risperidone. (Ipser & Stein, 2012) Evidence for the effectiveness of benzodiazepines is largely absent, despite their continued use in clinical practice. The α1 antagonist prazosin and the atypical antipsychotics has shown some efficacy in treatment-resistant PTSD. (Ipser & Stein, 2012)

The Psychological Aspect of Medication

Particularly in psychiatric medicine, the psychology that surrounds a medication can have a very profound impact on the effectiveness of the medication. The same applies to some extent also to psychotherapy. Expectations and beliefs affect the framework in which change can take place as well as its dynamics. In a study by Reger and colleagues, relative to exposure therapies, soldiers reacted to medications with significantly stronger agreement to scales reflecting embarrassment and shame for

seeking a particular form of treatment, negative occupational and career impact, and perceived debasement for seeking the treatment. They were significantly less willing to recommend medication treatment and had significantly less confidence and belief in the efficacy of medications. (Reger et al., 2013)

Comorbidity

Among all US veterans who received a diagnosis of PTSD, about 78% were given only a diagnosis of PTSD, while 22% had a dual diagnosis and a substance use disorder. Veterans with dual diagnoses were more likely to have been homeless and to have received a VA disability pension. Severe medical and psychiatric illness seems more common among veterans with dually diagnosed PTSD and substance use disorder compared to those with PTSD alone. (Bowe & Rosenheck, 2015) A PTSD diagnosis has also been reported to be associated with an increased risk for dementia diagnosis that varied with receipt of psychotropic medications. (Mawanda, Wallace, McCoy, & Abrams, 2017)

Alcohol and Substance Abuse

Posttraumatic stress disorder (PTSD) and alcohol/substance use disorder (A/SUD) are frequently comorbid. Comorbidity is associated with poorer psychological, functional, and treatment outcomes than either disorder alone. This review outlines biological mechanisms that are potentially involved in the development and maintenance of comorbid PTSD and A/SUD including neurotransmitter and hypothalamic–pituitary–adrenal dysregulation, structural differences in the brain, and shared genetic risk factors. The literature regarding pharmacological treatments that have been investigated for comorbid PTSD and A/SUD is also reviewed. Empirical data for each proposed mechanism and pharmacological approach is reviewed with the goal of making recommendations for future research. (Norman et al., 2012)

Neurobiology

In PTSD, pharmacological agents aimed at dampening (excessive) fear responses and facilitating the therapeutic alliance seem especially appropriate. The prevailing neurocircuitry model of PTSD postulates amygdala hyperactivity and ventromedial prefrontal cortex (vmPFC) hypoactivity toward both trauma-related and non-trauma-related stimuli (Pitman et al, 2012). Pharmacotherapy may reduce structural abnormalities in PTSD, while psychotherapy may decrease amygdala activity and increase prefrontal, dorsal anterior cingulate and hippocampus activations, that may relate to extinction learning and re-appraisal. A meta-study by Thomaes and colleagues showed that pharmacotherapy improved structural abnormalities in the form of increased hippocampus volume in

both adult-trauma and child abuse related PTSD. Adult-trauma PTSD patients showed decreased amygdala and increased dorsolateral prefrontal activations post. In a study with child abuse patients, no changes in the amygdala were observed, but decreased dorsolateral prefrontal, dorsal anterior cingulate and insula activation post-treatment. (Thomaes et al., 2014)

Hippocampus

PTSD appears to lead to decreased hippocampal volume. Numerous imaging studies have reported smaller hippocampal volumes in patients with PTSD. In a study with 55 combat veterans, Chao and colleagues found that PTSD duration was significantly associated with right hippocampal volume after accounting for intracranial volume, age, gender and comorbidities. (Chao, Yaffe, Samuelson, & Neylan, 2014)

Amygdala

Amygdala reactivity predicted symptom reduction during a treatment with trauma focused CBT. Adolescent girls with greater symptom reduction had greater amygdala reactivity to threat versus neutral images. Adolescent girls with poorer symptom reduction had greater amygdala reactivity to both threat and neutral images. (Cisler et al., 2015)

PTSD patients showed an enhanced amygdala activity compared to healthy controls, in an emotional face-matching task. This amygdala overactivity correlated with patients' symptom severity and anxiety levels. Patients also showed a problem disengaging their attention from threat cues on a DOT task. This attentional bias correlated with patients' anxiety levels. Amygdala activity causally correlated with the attentional bias in PTSD, and subsequent modulated anxious symptomatology. (El Khoury-Malhame et al., 2011)

Hypothalamic Pituitary Adrenal (HPA) Axis

Questions of how altered functioning of the hypothalamic pituitary adrenal (HPA) axis contribute to the development and maintenance of posttraumatic stress disorder (PTSD) have been the focus of extensive animal and human research. However, results have been inconsistent across studies, likely due to a variety of confounding variables, such as the effects of early life stress, biological sex, and the glucocorticoid used for interventions. (Dunlop & Wong, 2019)

According to a meta-analysis of functional connectivity studies in PTSD, amygdala hyperactivity in PTSD patients was predominantly observed in response to negative, non-trauma-related stimuli (Hayes et al, 2012; Sripada et al, 2012). This may result in decreased prefrontal control over the fear response and hence excessive fear in PTSD patients (Rauch et al, 2006).

Greater amygdala reactivity during extinction learning in PTSD patients has been associated with impaired extinction recall the next day (Milad et al, 2009). In PTSD, greater amygdala reactivity to fearful faces (Bryant et al, 2008) and negative pictures (van Rooij et al, 2015) before treatment predicted worse treatment outcome. In addition, effective exposure therapy was associated with

decreased amygdala and enhanced ventromedial prefrontal cortex activity toward emotional faces over the course of treatment (Felmingham et al, 2010).

Oxytocin

The neuropeptide oxytocin has both anxiolytic (Heinrichs et al, 2003) and pro-social (Olff, 2012) properties, which may make it useful in the treatment of PTSD. Oxytocin has anxiolytic properties both at the neurobiological and behavioral level. (Koch et al., 2016) Repeated intranasal oxytocin appears to be a promising early preventive intervention for PTSD for individuals at increased risk for PTSD due to high acute symptom severity. (Frijling, 2017) The neurobiological correlates of PTSD involve enhanced salience processing (i.e. amygdala, dorsal anterior cingulate cortex (dACC) and anterior insula (AI) hyperactivity), and reduced top-down inhibitory control over this fear response (i.e. dorsal and ventromedial prefrontal cortex (vmPFC) hypoactivity and diminished structural and functional connectivity between the vmPFC, hippocampus and amygdala). (Koch et al., 2014)

Substance P and Neurokinins

Substance P is a key first responder to many stressful and noxious stimuli, which could endanger the integrity of the organism. The molecule is rapidly released and may continue to be released depending on the presence of the stressor. The substance P-neurokinin-1 receptor (SP-NK1R) system has been extensively studied in experimental models of stress, fear, and reward. Elevated cerebrospinal fluid substance P levels have been noted in combat-related PTSD.

Communication

In a study by Felmingham and colleagues, PTSD participants rated happy facial expression as less intense than trauma-exposed controls. They also revealed lower activation to happy (-neutral) faces in the ventral striatum and a trend for reduced activation in the left amygdala. A significant negative correlation was found between emotional numbing symptoms in PTSD and right ventral striatal regions after controlling for depression, anxiety and PTSD severity. (Felmingham et al., 2014)

Prescribed Medication

Medication can a valuable support in facilitating psychotherapy. And that is how it should largely be viewed. Medication by itself can stabilize symptoms and make patients more functional and even feel improvements in their mood and anxiety, but it tends to be vastly inferior in the long run as compared to a combination of medication and psychotherapy. (Haverkampf, 2018a)

One paramount problem of medication for PTSD is that the quality of empirical data is not as good as in many other areas of psychiatry, another that PTSD can manifest in so many different forms that a manualized approach with strict guidelines may be of limited use in the individual case. It may thus be

no surprise that in the US, veterans with PTSD were frequently prescribed medications not supported by existing guidelines. (Abrams, Lund, Bernardy, & Friedman, 2013)

Abrams and colleagues found that in 2009, among all veterans with PTSD who had continuous VA medication use, second-generation antipsychotics were prescribed for 25.6% of these veterans and benzodiazepines were prescribed for 37.0% of the sample. In a 2012 study, the prescriptions for antipsychotics and benzodiazepines showed a significant decline since 1999. Nonbenzodiazepine hypnotic prescribing tripled when zolpidem was added to the VA national formulary in 2008. Buspirone prescribing decreased steadily, while prazosin prescribing expanded nearly 7-fold. (Bernardy, Lund, Alexander, & Friedman, 2012)

There are several guidelines for the pharmacological treatment of posttraumatic stress disorder (PTSD) in primary care, such as the one by the World Federation of Biological Psychiatry (WFSBP) (Bandelow et al., 2012) and many others.

SSRIs and SNRIs

Medication treatments can be effective in treating PTSD, acting to reduce its core symptoms, as well as associated depression and disability. In a 2006 Cochrane review, support was found for the status of selective serotonin reuptake inhibitors (SSRIs) as first line agents in the pharmacotherapy of PTSD, as well as their value in long-term treatment. (D. J. Stein, Ipser, Seedat, Sager, & Amos, 2006) Multisite randomized clinical trials (RCTs) have noted the efficacy of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) for PTSD treatment. (Bernardy & Friedman, 2015) In a study by Schneier and colleagues, treatment with paroxetine plus prolonged exposure was more efficacious than prolonged exposure plus placebo for PTSD related to the World Trade Center attack. (Schneier et al., 2012) It has been reported that sertraline is a front-line medication for PTSD which also shows an impact on drinking outcomes. (Hien et al., 2015)

SSRIs probably exert their effects by remediating emotion regulatory brain activity. Individual differences in patient response might be explained, in part, by pre-treatment differences in neural systems supporting the downregulation of negative affect. In a study by MacNamara and colleagues less activation of the right ventrolateral PFC and inferior frontal gyrus during pre-treatment emotion regulation was associated with greater reduction in PTSD symptoms with SSRI treatment, irrespective of pre-treatment severity. Patients with the least recruitment of prefrontal emotion regulatory brain regions may benefit most from treatment with SSRIs, which appear to augment activity in these regions. (MacNamara et al., 2016)

In a study by Schneier and colleagues, the data suggested that using a combination of sertraline plus mirtazapine may have clinically meaningful advantages in symptomatic improvement, relative to SSRI treatment alone. Both treatments were reportedly well-tolerated, with significantly increased appetite but not weight gain in the combined treatment group. (Schneier et al., 2015)

Antipsychotics

Second generation antipsychotics seem to have some effect on individual symptoms of PTSD, while their overall effect on the condition may be relatively limited. PTSD is associated with metabolic syndrome and obesity, which can also be side effects of second-generation antipsychotics. Heppner and colleagues found that antipsychotic medication usage was not uniquely associated with elevated risk of metabolic syndrome when PTSD severity and other sociodemographic, psychiatric, and behavioral variables were accounted for. Furthermore, PTSD severity continued to be a significant and unique predictor of risk for metabolic syndrome. (Heppner et al., 2012) In a 2011 review of eighteen clinical trials (10 double-blind placebo-controlled, eight open-label) of atypical antipsychotics for PTSD, the effect sizes of double-blind placebo-controlled trials were small, but were positive for risperidone and quetiapine. Intrusive and hypervigilance symptom subscales showed the most improvement. (Ahearn, Juergens, Cordes, Becker, & Krahn, 2011) In a 6-month, randomized, double-blind, placebo-controlled study of 247 patients with military-related PTSD and serotonin reuptake inhibitor resistant symptoms, risperidone compared with placebo did not reduce PTSD symptoms. (Krystal et al., 2011) In a 2002 study with 19 patients with PTSD who were minimally responsive to 12 weeks of treatment with an SSRI at maximum tolerated dose, olanzapine augmentation was associated with statistically significantly greater reduction than placebo in specific measures of posttraumatic stress, depressive, and sleep disorder symptoms. Clinician-rated global response rates did not, however, significantly differ between groups. (M. B. Stein, Kline, & Matloff, 2002)

Some empirical data indicates that topiramate and prazosin may be effective in reducing PTSD and alcohol use disorder (AUD) symptoms in individuals with comorbidity. (Petrakis, Ralevski, & Olivera-Figueroa, 2014)

The efficacy of other behavioral and alternative treatments (mindfulness-based, yoga, and acupuncture) is more difficult to evaluate since the evidence comes from small, single studies without comparison groups. (Petrakis et al., 2014)

Intranasal oxytocin

A lack of social support and recognition by the environment is one of the most consistent risk factors for posttraumatic stress disorder (PTSD), and PTSD patients will recover faster with proper social support. The oxytocin system has been proposed to underlie beneficial effects of social support as it is implicated in both social bonding behavior and reducing stress responsivity, notably amygdala reactivity (Koch et al., 2014; Olff et al., 2010; Olff, 2012). The amygdala is found to be hypersensitive in people with PTSD. In this presentation, we present the BOOSTER results on the effects of a single oxytocin administration on amygdala reactivity in response to emotional faces in PTSD patients versus traumatized controls. We found significantly decreased bilateral amygdala reactivity towards emotional faces in PTSD patients compared to traumatized controls. These promising results call for

intervention studies such as studying the effects of medication (oxytocin) enhanced psychotherapy in PTSD patients. (Olff et al., 2014)

Oxytocin appears to have a positive effect in PTSD patients. Under placebo, the expected valence-dependent amygdala reactivity (ie, greater activity toward fearful-angry faces compared with happy-neutral faces) was absent in PTSD patients. In a study by Koch and colleagues, oxytocin administration dampened amygdala reactivity toward all emotional faces in male and female PTSD patients, but enhanced amygdala reactivity in healthy male and female trauma-exposed controls, independent of sex and stimulus valence. In PTSD patients, greater anxiety prior to scanning and amygdala reactivity during the placebo session were associated with greater reduction of amygdala reactivity after oxytocin administration. (Koch et al., 2016)

Dampening the exaggerated fear response (i.e. by reducing amygdala hyperactivity) and enhancing top-down inhibitory control (i.e. by promoting prefrontal control over the amygdala) during psychotherapy is an important target for medication-enhanced psychotherapy (MEP) in PTSD patients. Since the neuropeptide oxytocin has been found to act on these two processes, we propose that OT is a promising pharmacological agent to boost treatment response in PTSD. Human fMRI studies indicate that intranasal oxytocin attenuates amygdala (hyper)activity and enhances connectivity of the amygdala with the ventromedial prefrontal cortex and hippocampus, resulting in increased top-down control over the fear response. In addition, intranasal oxytocin was found to attenuate amygdala–brainstem connectivity and to change activity and connectivity in nodes of the salience network (i.e. AI and dACC). Furthermore, oxytocin administration may modulate hypothalamus–pituitary–adrenal (HPA) axis and autonomic nervous system (ANS) function and may enhance social behavior, which could be beneficial in the therapeutic alliance. We also discuss contextual and interindividual factors (e.g. gender and social context) which may influence the effectiveness of oxytocin in MEP. In all, we propose that intranasal oxytocin given prior to each psychotherapy session may be an effective additive treatment to boost treatment response in PTSD. (Koch et al., 2014)

In a 2018 randomized, placebo-controlled, double-blind study, Prolonged Exposure (PE) therapy was combined with weekly oxytocin doses. Findings supported the feasibility and safety of oxytocin combined with PE. (Flanagan, Sippel, Wahlquist, Moran-Santa Maria, & Back, 2018)

Anticonvulsant Medication

Anticonvulsants have been studied for many indications, including posttraumatic stress disorder (PTSD). The limited efficacy research on anticonvulsants for PTSD is mixed. However, anticonvulsants are prescribed widely to Veterans with PTSD. Our objective was to measure trends and factors associated with anticonvulsant prescription among Veterans with PTSD. Although 24.9% of patients in the cohort received an anticonvulsant during their initial year of PTSD treatment, 94.6% had an indication unrelated to PTSD and 51.2% initiated anticonvulsant use before their PTSD diagnosis.

While there was growth in anticonvulsant initiation over the 10-year period, this was explained both by growth in indications unrelated to PTSD and increased use of anticonvulsants for these indications. The rate of anticonvulsant initiation without an indication was stable at approximately 5% throughout the period, with patient and service use characteristics driving the selection of individual agents. A large and increasing proportion of Veterans with PTSD receive anticonvulsant prescriptions. However, this may be appropriate use driven by increased prevalence of comorbid conditions that may be an indication for anticonvulsant use, including pain and headache disorders. (Shiner, Westgate, Bernardy, Schnurr, & Watts, 2017)

Beta-Blockers

Some empirical data has offered support for the use of the beta-blocker propranolol to prevent posttraumatic stress disorder (PTSD). It appears that propranolol can block memory reconsolidation in PTSD patients, which could reduce symptoms. (Taibi, 2019) However, this direction of research still seems to be in its infancy.

Nugent and colleagues conducted a study in children, in which twenty-nine injury patients aged 10 to 18 at risk for PTSD were randomized to a double-blind 10-day trial of propranolol versus placebo. Six-week PTSD symptoms and heart rate were assessed. Although intent-to-treat analyses revealed no group differences, findings showed that girls receiving propranolol reported more PTSD symptoms while boys receiving propranolol showed a nonsignificant trend toward fewer PTSD symptoms (Nugent et al., 2010)

Newer Approaches

Posttraumatic stress disorder (PTSD) is a common condition for which existing treatments are ineffective for many patients. Recent discoveries in the neurobiology of learning and memory, along with expanding knowledge of how those systems are impacted by the biology of the stress response, have opened new arenas for potential medication treatments for PTSD. We conducted a review of registered clinical trials investigating the efficacy of new agents for PTSD. The glucocoritcoid and adrenergic signaling systems are the most frequent targets of these investigational approaches to the prevention and treatment of PTSD. Additional trials are evaluating modulation of other CNS targets, including neurosteroids, glutamate, gamma-amino butyric acid, endocannabinoids, oxytocin, neurokinin/Substance P, and dopamine. A particularly exciting area of research is studies examining Medication-Enhanced Psychotherapy (MEP). Medications provided before or after exposure therapy for PTSD can enhance outcomes by: 1) strengthening learning and memory of fear extinction; 2) disrupting reconsolidation, thereby weakening fear memories; or 3) facilitating engagement in psychotherapy by reducing fear and enhancing openness to experience. The next few years promise

to produce insight into the neurobiology and clinical efficacy of several novel approaches in the pharmacologic treatment and prevention of PTSD. (W. Dunlop, Mansson, & Gerardi, 2012)

Endocannabinoids

The endocannabinoid system seems to provide an avenue for evidence-based treatment development for PTSD. (Neumeister, 2013) In a double-blind RCT with the synthetic endocannabinoid nabilone, a reduction in PTSD-related nightmares was shown. The medication was reportedly well tolerated. (Jetly, Heber, Fraser, & Boisvert, 2015)

Substance P and Neurokinin Antagonists

An RCT with the selective NK1R antagonist GR205171 in predominately civilian PTSD showed a significant improvement in the mean CAPS total score across all patients over time, but no significant difference was found between GR205171 and placebo. Likewise, there was no significant effect of drug on the proportion of responders. GR205171 had fewer adverse effects but was thus not significantly superior to placebo in the short-term treatment of chronic PTSD. (Mathew et al., 2011) An exploratory analysis, however, showed that GR205171 treatment was associated with significant improvement compared to placebo on the CAPS hyperarousal symptom cluster.

Glucocorticoids

Hydrocortisone given to prevent PTSD following a trauma is apparently the best supported HPA axis intervention for PTSD. (Dunlop & Wong, 2019) The use of traumatic memory reactivation temporally paired with glucocorticoid administration has been reported to show some promise as a further therapeutic option. (Surís, North, Adinoff, Powell, & Greene, 2010)

Self-Medication

Three explanations for the comorbidity of PTSD and substance use disorder (SUD) can usually be found in the literature (Stewart & Conrod, 2008).:

- the self-medication hypothesis
- the substance-induced anxiety enhancement hypothesis, and
- the shared vulnerability hypothesis

According to the self-medication hypothesis, PTSD temporally precedes SUD and leads to the development of substance use problems as the individual attempts to self-medicate the negative affect associated with his or her trauma symptoms. In contrast, the substance-induced anxiety enhancement hypothesis maintains that SUD leads to the development of PTSD symptoms following trauma because SUDs affect the functioning of the body's stress response system. Finally, the shared vulnerability hypothesis maintains that PTSD and SUD onset occur near the same time because of a

shared vulnerability common to the development of both disorders. (Hruska & Delahanty, 2013) In a study by Hien and colleagues, PTSD severity reductions were more likely to be associated with substance use improvement, with minimal evidence of substance use symptom reduction improving PTSD symptoms. There is support for the self-medication model of coping with PTSD symptoms (Hien et al., 2010) Trauma-exposed individuals are likely engaging in adaptive and maladaptive coping strategies, the latter of which may be compounding distress. In a study by Sheerin and colleagues, PTSD was associated with increased likelihood of self-medication, while alcohol abuse was associated with decreased likelihood of help-seeking. When self-medication was included as a predictor, PTSD was no longer associated with help seeking, although alcohol abuse remained inversely associated. (Sheerin et al., 2016) In a study by Simpson and colleagues, results generally supported a self-medication model with elevated PTSD symptoms predictive of greater alcohol use on that same day and on the following day, while drinking did not predict next-day PTSD symptoms. (Simpson, Stappenbeck, Luterek, Lehavot, & Kaysen, 2014)

Alcohol

In a study by Ullman, child sexual abuse was related to greater PTSD and problem drinking. Revictimization predicted PTSD and problem drinking over time. PTSD did not directly affect problem drinking over time. Revictimization partially mediated the effect of child sexual abuse on PTSD and problem drinking. Revictimization predicted PTSD over time but not problem drinking consistently. (Ullman, 2016)

Structural equation models showed disconstraint to meditate the path from PTSD symptoms to alcohol problems, supporting a trait vulnerability conceptualization. Findings regarding negative emotionality and self-medication were more mixed. Negative emotionality played a stronger role in cross-sectional than in prospective analyses, suggesting the importance of temporal proximity. Self-regulation skills may be an important focus for clinicians treating PTSD symptoms and alcohol misuse disorders concurrently. (Read, Merrill, Griffin, Bachrach, & Khan, 2014)

In this study of patients with alcohol dependence and PTSD, naltrexone treatment resulted in a decrease in the percentage of days drinking. Prolonged exposure therapy was not associated with an exacerbation of alcohol use disorder. (Foa et al., 2013)

Opioids

Opioid use disorder is an uncommon but increasing comorbidity among patients with PTSD. Patients entering VA treatment for PTSD have their opioid use disorder treated with opioid agonist treatments in large and increasing numbers. (Shiner, Leonard Westgate, Bernardy, Schnurr, & Watts, 2017)

Prevention

In a Cochhrane study by Amos and colleagues, there was moderate quality evidence for the efficacy of hydrocortisone for the prevention of PTSD development in adults. They found no evidence to support the efficacy of propranolol, escitalopram, temazepam and gabapentin in preventing PTSD onset. The findings were, however, based on a few small studies with multiple limitations. (Amos, Stein, & Ipser, 2014)

End of Life Care

There are good indications that PTSD treatment should also continue at end of life. A retrospective pilot study by Kelly-Cook and colleagues with terminally ill Vietnam Veterans with a history of PTSD showed that 72% of participants with PTSD used benzodiazepines, hypnotics, antidepressants, and antipsychotic medications versus 40% of the non-PTSD participants. There was significant correlation between a lifetime diagnosis of PTSD with antidepressant use and hypnotics during end of life care but not with benzodiazepines or antipsychotics. (Kelley-Cook, Nguyen, Lee, Edwards, & Sanchez-Reilly, 2016)

Psychotherapy

Prolonged Exposure (PE), Cognitive Processing Therapy (CPT) and trauma-focused Cognitive Behavioral Therapy (CBT) have a large evidence base and are trauma-focused, which means they directly address memories of the traumatic event or thoughts and feelings related to the traumatic event. (Watkins, Sprang, & Rothbaum, 2018) It has been reported that veterans with PTSD benefit less from psychotherapy than other populations. (Haagen, Smid, Knipscheer, & Kleber, 2015) On the other hand, it is possible that trauma-focused CBT, for example, has an enduring effect lasting beyond the end of treatment that may not be found with antidepressant medication. (Hollon, 2019) Trauma-focused therapists also frequently note that although their patients can be traumatized again, once a given trauma is adequately treated, the symptoms typically do not come back in the absence of new trauma. (Hollon, 2019)

Therapeutic Alliance

As far as medication is concerned, compliance can be affected by several psychological factors that may be influenced by the PTSD symptoms, including a loss of trust in others, as well as the conditions that may be comorbid, such as depression or anxiety. For example, it has been reported that concerns about medications explain a significant proportion of the association between PTSD symptoms and non-adherence to medication in stroke survivors. (Edmondson, Horowitz, Goldfinger, Fei, & Kronish, 2013)

In psychotherapy, the therapeutic alliance between therapist and patient may be even more important to lead to a successful treatment outcome. One reason is that the alliance has an impact on the communication patterns and dynamics between patient and therapist, which in turn largely determine the outcome of therapy (Haverkampf, 2018b). Early alliance is important for treatment adherence and completion and should be routinely assessed by clinicians. In a study by Keller and colleagues, trauma-related social support predicted the strength of early alliance beyond the effects of treatment condition, while a history of childhood sexual abuse was not predictive of a lower early alliance. (Keller, Zoellner, & Feeny, 2010) Alliance plays a significant role in Communication-Focused Therapy®, where it is seen to grow out of the communication dynamics between therapist and patients. Developing awareness and insight for communication patterns can help increase the alliance and create greater clarity on how to achieve the objectives of a course of therapy (Haverkampf, 2017a).

Exposure Therapy

In case of a comorbid depression, IE was significantly less preferred than medication. Also, IE was significantly more likely to be offered when patients expressed a preference for trauma-focused treatment. The therapist factors were also found to be importantly related to treatment preferences, with high credibility in the technique being positively related to the therapists' preference for IE. Perceived barriers to IE, such as a fear of symptom exacerbation and dropout, were negatively related to the perceived suitability of the treatment when patients had suffered multiple traumas in childhood. (van Minnen, Hendriks, & Olff, 2010) Gains from prolonged exposure have been reported to be largely maintained across a 24-month follow-up, with responders to prolonged exposure offered up to two booster sessions, whereas nearly all of the antidepressant medication responders were kept on medication (Hollon, 2019)

EMDR

Eye movement desensitization and reprocessing (EMDR) was developed by Francine Shapiro starting in 1988 in which the person being treated is asked to recall distressing images; the therapist then directs the patient in one type of bilateral stimulation, such as side-to-side eye movements or hand tapping. It is “based on the idea that negative thoughts, feelings and behaviors are the result of unprocessed memories. The treatment involves standardized procedures that include focusing simultaneously on (a) spontaneous associations of traumatic images, thoughts, emotions, and bodily sensations and (b) bilateral stimulation that is most commonly in the form of repeated eye movements." (WHO, 2013) In one relevant study trauma-focused therapy (in this instance, eye movement desensitization and reprocessing) had an enduring effect not found for antidepressant medication. (Hollon, 2019) In a study by Lee and colleagues, the effectiveness of Stress Inoculation Training with Prolonged Exposure (SITPE) was compared to Eye Movement Desensitization and Reprocessing (EMDR) in twenty-four participants with PTSD. On global PTSD measures, there were no significant differences between the treatments at the end of therapy. However, on the subscale

measures of the degree of intrusion symptoms, EMDR did significantly better than SITPE. At follow-up EMDR was found to lead to greater gains on all measures. (Lee, Gavriel, Drummond, Richards, & Greenwald, 2002) In another study with 74 rape victims and 20 control participants, prolonged exposure and EMDR did not differ significantly for change from baseline to either posttreatment or 6-month follow-up measurement for any quantitative scale. (Rothbaum, Astin, & Marsteller, 2005) In a study on 60 participants, EMDR and relaxation did not differ from one another in speed or efficacy, while exposure therapy led to significantly less avoidance and reexperiencing symptoms and resulted in a greater proportion of participants who no longer met criteria for PTSD after treatment. (Taylor et al., 2003) In children, EMDR has shown in at least one study a significant improvement in re-experiencing symptoms. (Ahmad, Larsson, & Sundelin-Wahlsten, 2007)

Seeking Safety

Seeking safety is a present-focused cognitive–behavioral therapy for co-occurring PTSD and alcohol use disorder (AUD). Seeking safety has had mixed efficacy in clinical trials. (Petrakis et al., 2014) Hien and colleagues conducted a randomized controlled trial to test the benefit of combining Seeking Safety with sertraline, a front-line medication for PTSD shown to also impact drinking outcomes. Seeking safety and sertraline led to a significantly greater reduction in PTSD symptoms than seeking safety with placebo at end-of-treatment, which was sustained at 6- and 12-month follow-up, while there were no significant differences whether sertraline or placebo where combined with seeking safety. (Hien et al., 2015)

Group Therapy

In a group with participants with a similar condition, a patient can see that they are not alone in their struggles and that others may be facing similar seemingly unsurmountable challenges and setbacks as they do themselves. There are also the advantages of learning from and giving back to others, which can both be important in their own right. Groups can provide additional social support and promote awareness for communication patterns and dynamics that can be positive, albeit sometimes also unhelpful, for the individual participant (Haverkampf, 2017b).

Research has found limited evidence that PTSD can be successfully treated in a group format (Institute of Medicine, 2008). Haagen and colleagues performed meta-analyses to identify psychotherapy efficacy predictors. Group-only therapy formats should not be used to treat PTSD. Exposure therapy and CPT are preferred above SMT and EMDR. Patients with low and high PTSD symptom severity levels risk lower treatment gains. (Haagen et al., 2015) Resick and colleagues conducted a study to determine whether group therapy improves symptoms of posttraumatic stress disorder (PTSD). The randomized clinical trial compared efficacy of group cognitive processing therapy (cognitive only version; CPT-C) with group present-centered therapy (PCT) for active duty military personnel. Both treatments resulted in large reductions in PTSD severity, but improvement was greater in CPT-C. CPT-C also reduced depression, with gains remaining during follow-up. In PCT, depression only improved

between baseline and before the first session. There were few adverse events associated with either treatment. (Resick et al., 2015)

Other Therapies

Barned and colleagues studied whether the regular practice of Transcendental Meditation (TM) decreased the need for psychotropic medications required for anxiety and post-traumatic stress disorder (PTSD) management and increased psychological wellbeing in 74 military Service Members. At 1 month, 83.7% of the TM group stabilized, decreased, or ceased medications and 10.8% increased medication dosage; compared with 59.4% of controls that showed stabilizations, decreases, or cessations; and 40.5% that increased medications. A similar pattern was observed after 2 and 6 months. The control group also seemed to experience an increase in symptom severity compared with the group practicing TM. (Barnes, Monto, Williams, & Rigg, 2016)

Psychotherapy and Medication

It is quite clear from study data and clinical experience that medication can offer some support in the treatment of PTSD, but that psychotherapy should always be considered the first-line treatment and medication as a valuable and potentially quite helpful add-on. Unfortunately, mental compartmentalization in the choice of effective treatment constellations in clinical practice and research often hinders the formulation of an effective treatment plan. Few studies have, for example explored, how best to combine a particular psychotherapy with a specific type of medication. But that would be desperately needed.

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PTSD AND MEDICATION

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