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Translating Molecular and Neuroendocrine Findings in PTSD and Resilience to Novel Therapies

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Abstract

Many biological systems are altered in association with Posttraumatic Stress Disorder (PTSD) and resilience. However, there are only few approved pharmacological treatments for PTSD, and no approved medications to enhance resilience. This paper provides a critical review of select neurobiological findings in PTSD and resilience, and also of pharmacologic approaches that have emerged from this work. The medications summarized involve engagement with targets in the adrenergic, the hypothalamic-pituitary-adrenal (HPA) axis, and neuropeptide Y (NPY) systems. Other highlighted approaches involve the use of ketamine and 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy, which recently surfaced as promising strategies for PTSD though the neurobiological mechanisms underlying their actions, including for promoting resilience, are not yet fully understood. The former approaches fall within the broad concept of "rational pharmacotherapy" in that they attempt to directly target dysregulated systems known to be associated with post-traumatic symptoms. To the extent that use of ketamine and MDMA promote symptom improvement and resilience in PTSD, this provides an opportunity for reverse-translation and identification of relevant targets and mechanism of action through careful study of biological changes resulting from these interventions. Promoting resilience in trauma-exposed individuals may involve more than pharmacologically manipulating dysregulated molecules and pathways associated with developing and sustaining PTSD symptom severity, but also producing a substantial change in mental state that increases the ability to engage with traumatic material in psychotherapy. Neurobiological examination in the context of treatment studies may yield novel targets and promote a greater understanding of mechanisms of recovery from trauma.

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Dr. Feder is named co-inventor on a patent application in the US, and several issued patents outside the US filed by the Icahn School of Medicine at Mount Sinai related to the use of ketamine for the treatment of post-traumatic stress disorder (PTSD). This intellectual property has not been licensed. Dr. Yehuda is listed as co-inventor on a US patent pertaining to genetic testing in PTSD. Drs. DePierro and Lepow reported no biomedical financial interests or potential conflicts of interest.

Keywords

PTSD; Resilience; Pharmacotherapy; Ketamine; MDMA; Glucocorticoids

Introduction

Shortly after the appearance of PTSD in the psychiatric nosology (1), and again more recently (2), Friedman suggested that optimal pharmacotherapy for PTSD would result from targeting unique features of its pathophysiology. Friedman's original statement was made when little was known about the biology of PTSD, but many believed its distinct clinical presentation and relationship to environmental exposure would necessitate novel treatments. As early neurochemical and neuroendocrine findings in PTSD emerged, it seemed reasonable to develop pharmacotherapeutic strategies based on reversing the observed dysregulation.

Despite evidence implicating numerous biological systems in PTSD (3-6), there are few medications with demonstrated efficacy. The lack of pharmacologic strategies following great investment in translational and biological studies is thought by some to constitute a crisis (7). Fortunately, advances in understanding the neurobiology of resilience offered potentially new targets associated with trauma recovery or promotion of post-traumatic growth. These findings include mechanisms involved in brain plasticity and cognition that could be targeted to lessen the severity of PTSD symptoms and facilitate a change in perspective or meaning (3, 4). For the purpose of this review, resilience is defined broadly as the ability to adapt to adversity and trauma (4), ranging from resistance to bouncing back from trauma exposure to recovery from PTSD, the latter often involving restorative/re-integrative processes of healing accomplished via successful treatment (8, 9).

Currently approved medications for PTSD are limited to selective serotonin reuptake inhibitors (SSRIs), initially tested because of their effectiveness in depression, and therefore not a reflection of the vision of a rational pharmacotherapy based on a translational model of discovery. Table 1 provides a summary of compounds that have been examined and the targets hypothesized to explain their actions (see Supplement for an elaborated version of the table).

That advances in the neurobiology of PTSD have not led to novel treatment approaches raises questions concerning the extent to which a translational approach that identifies, and then seeks to reverse, perturbed biological systems associated with PTSD symptoms will yield treatments that produce sufficient recovery from the effects of trauma for the majority of patients. Traumatic exposures result not only in behavioral symptoms, but in a disruption of the survivor's world views, priorities, and interests. Developing this change in outlook might require activating resilience-related pathways that are distinct from those that contribute to behavioral symptoms.

In considering how neuroscience has, and will continue, to catalyze treatment development in PTSD it should be noted that current treatment guidelines (10, 11) have uniformly designated psychotherapy, particularly cognitive behavioral therapy (CBT), as a first line

treatment. CBT is thought to be supported by translational models involving fear extinction, and may therefore reflect a target-driven treatment for PTSD (12, 13). Recent research has demonstrated effects in normalizing disrupted patterns in brain connectivity (14). While questions remain about whether a single course of CBT is sufficient to achieve recovery for survivors with extreme or repeated trauma (15, 16), that psychotherapy alters dysregulated biological circuits provides an object lesson for translational neuroscience inviting inquiry into a broader set of targets that might work in synergy with pharmacotherapy. Currently, pharmacotherapy is recommended as an adjunct to psychotherapy, or an approach when psychotherapy is not available (10, 17), with the caveat that medications constitute “low effect” treatments (11).

In clinical practice many patients with PTSD are prescribed psychotropic medications without psychotherapy either because the patient does not want, failed to respond, dropped out, or had adverse reactions, to psychotherapy. Physicians often use medications off label and/or prescribe several medications concurrently. Yet many patients remain chronically symptomatic. The failure to successfully treat PTSD with pharmacotherapy alone may reflect that the ultimate biological targets for PTSD symptom reversal have not been identified, or that clinically-relevant subtyping has yet to inform personalized therapeutic options. Target activation with the medication may be enhanced through engagement with the traumatic material. Bringing the traumatic memory into consciousness may even activate similar biological circuits to those targeted by medications. However it is not currently known whether pharmacological activation of these same circuits would yield similar effects as psychotherapy (18). Alternatively, medications may activate biological targets that might maximize response to trauma-focused psychotherapy.

This review examines selected molecular and neuroendocrine findings in PTSD and resilience from the perspective of rational pharmacotherapy. It also examines how identification of biological targets may come about using neurobiological analysis of treatments that have not been born from traditional rational pharmacotherapy approaches.

Candidate Therapeutic Targets

Adrenergic System

Initial studies in PTSD showed increased sympathetic nervous system (SNS) arousal and elevated basal levels of catecholamines such as norepinephrine (19-22). Furthermore, administration of the alpha$_2$-receptor antagonist yohimbine precipitated flashbacks (23). Subsequent studies confirmed central and peripheral noradrenergic system involvement in trauma-related processes, including fear and extinction learning, depression, anxiety and resilience (22, 24).

Medications targeting central and peripheral adrenergic hyperactivity, such as alpha$_2$ agonists clonidine and guanfacine, have met with limited success (25, 26). An exception is the alpha$_1$ adrenoreceptor antagonist prazosin, which showed a signal for treatment of nightmares (27). The promising results of initial prazosin trials (28) led to fairly broad use of the drug in Veteran Affairs and private settings (e.g. (29)), though a recent large scale study did not show efficacy for prazosin above placebo in moderating nightmare severity (30). The

β-adrenergic receptor blocker propranolol has been of interest in the context of blocking the consolidation or reconsolidation of traumatic memories (31). Propranolol decreased fear learning in animals (32), though data regarding its effect on emotional memory in people are less straightforward.

Given the importance of the adrenergic systems in mediating hyperarousal and re-experiencing symptoms in PTSD, as well as fear learning, extinction, and reconsolidation the lack of a translatable pharmacologic treatment for PTSD based on noradrenergic manipulation has been disappointing. The findings imply that reducing both central and peripheral SNS arousal directly might not be sufficient for promoting recovery; however, it remains plausible that individuals with clear adrenergic dysregulation (33) may benefit from these therapies

Although medications such as propranolol have not produced a robust treatment signal for treatment or prevention of PTSD (31), they might augment psychotherapy if used prior to reactivation of trauma memories (34). The question that arises is whether exposure therapies are enhanced or disrupted by manipulating arousal or distress at reminders during early phases of treatment. Reducing distress may help patients better access traumatic memories in therapy. However, initial distress might facilitate more powerful extinction or desensitization with subsequent exposures. Indeed, a single-dose of yohimbine prior to exposure therapy increased in-session subjective distress and physiological arousal, but produced lower heart rate reactivity to trauma reminders at one-week follow up, without influencing PTSD scores (35).

Glucocorticoid System

The hypothalamic-pituitary-adrenal (HPA) axis is the major constituent of the neuroendocrine response to acute and chronic stress and has been well characterized. Cortisol is involved in the regulation and containment of the SNS and parasympathetic responses to stress, both adaptive responses that help the body adapt to a stressor. The autoregulation of the normal stress response initiated by cortisol (through negative feedback inhibition) helps restore stress-related reactions to baseline after the termination of the acute stressor (36). An efficient negative feedback inhibition (secondary to enhanced glucocorticoid receptor (GR) responsiveness) results in attenuated cortisol elevations in response to stress, thereby increasing the body’s exposure to its own catecholamines (37) .

When HPA axis dysregulation has been noted in chronic PTSD, it is generally altered in a paradoxical direction with elevated corticotrophin-releasing hormone (CRH) levels despite decreased levels of cortisol. The cortisol response to dexamethasone is greater, reflecting enhanced responsiveness of GR in the pituitary (37-40). This profile differs from that observed in depression in which both elevated CRH and cortisol levels are present with diminished GR responsiveness (37). Differences in cortisol signaling in PTSD also contribute to abnormally reduced exposure of some afferent pathways to cortisol thereby contributing to increased sympathetic activation (41-43). Since catecholamines facilitate the consolidation of memories (44), and cortisol facilitates extinction and interferes with fear memory reconsolidation (45), suboptimal levels of cortisol in the face of greater SNS

activation might facilitate the formation of the durable traumatic memories that characterize PTSD (46).

Attempts to utilize HPA axis interventions in chronic PTSD are challenging because chronic administration of steroids in non-endocrine conditions can have unintended consequences, and is ill-advised when hormone levels are in the endocrinologically normal range. Ideal HPA interventions would be short term, and designed to recalibrate a dysregulated feedback loop. However, such strategies have not yielded powerful results to date. A multi-site phase II randomized clinical trial (RCT) of the GR antagonist, mifepristone, comprised of 600 mg daily dose for one week, indicated no overall advantage over placebo for PTSD symptoms (47). Subgroup analysis indicated that combat veterans without a history of mild TBI experienced significant symptom improvements with mifepristone. Dunlop et al. (48) showed no improvement in PTSD in a placebo-controlled trial of a CRH type-1 receptor antagonist. While targeting the HPA axis would appear to constitute a rational pharmacotherapy approach based on the unique alterations in PTSD, glucocorticoid-based treatments have not yielded significant treatment gains in chronic PTSD.

The HPA axis may, however, be a target for secondary PTSD prevention. A serendipitous observation that hydrocortisone as part of standard treatment following septic shock improved mental health outcomes (49) led to a controlled trial demonstrating that corticosteroids administered following major surgery resulted in higher quality of life 6 months later (50). Based on the idea that lower cortisol levels at the time of trauma exposure might facilitate SNS hyperactivity and lead to intrusive, traumatic memories, this strategy of glucocorticoid administration during the “golden hours” following trauma was used to identify its role in PTSD prevention (51, 52). A Cochrane review (53) concluded that hydrocortisone treatment in the acute aftermath of trauma is the only preventive pharmacological agent with a convincing evidence base now. If replicated, this treatment would constitute rational psychopharmacology for PTSD prophylaxis.

Augmentation of psychotherapy with hydrocortisone has also been examined to enhance reconsolidation of emotional memories working synergistically with prolonged exposure (PE), a cognitive behavioral therapy. An initial case report found greater improvement in PTSD symptoms post-exposure treatment relative to placebo (54), and a follow-up placebo-controlled study observed that responders to hydrocortisone augmentation had greater GR sensitivity at treatment initiation (55). Hydrocortisone administered immediately following an exposure therapy session resulted in lower avoidance and numbing symptoms one week later, when participants were experimentally presented with their trauma narratives (56). Interestingly, the synthetic glucocorticoid, dexamethasone, was found to have no added benefit in virtual-reality-based PTSD treatment in veterans, and was associated with greater drop-out relative to placebo (57). Unlike hydrocortisone, dexamethasone does not cross the blood-brain barrier, thus while dexamethasone reduces endogenous cortisol via negative inhibition at the pituitary, it may amplify low cortisol effects in the brain in a pathophysiologic direction.

Neuropeptide Y

Laboratory work since the 1990s has implicated neuropeptide Y (NPY) in modulating stress responses (for review, see (58)). NPY, a neuropeptide implicated in anxiety-related behavior, regulates HPA-axis activity by stimulating release of ACTH and corticosterone, and decreases SNS activity through inhibition of norepinephrine release from sympathetic noradrenergic neurons. An initial study conducted in soldiers during survival school training demonstrated increases in plasma NPY levels following uncontrollable stress in Special Forces soldiers, considered more resilient, than in non-Special Forces soldiers. Higher NPY levels during stress were associated with better behavioral performance scores, lower self-reported dissociation, and higher cortisol responses, suggesting that NPY might be associated with resilience during uncontrollable stress (59). Other studies demonstrated lower plasma NPY levels and blunted NPY response to yohimbine in men with combat-related PTSD (60), and higher plasma NPY levels in combat-exposed veterans who recovered from, compared to those who never had, PTSD (61). Veterans with chronic PTSD were also found to have lower concentrations of cerebrospinal fluid NPY relative to healthy controls (62). Moreover, individuals with the low NPY expression diplotype evidenced greater amygdala reactivity to fearful faces (63).

A recent small-scale study tested ascending-doses of intranasal NPY administration in a cross-over placebo-controlled study, and found that higher doses (e.g. 9.6 mg) were associated with greater reductions in self-reported anxiety following a trauma script symptom provocation (64). Additional studies are needed to evaluate the full potential of NPY for the treatment or prevention of PTSD. If effective, this treatment would also constitute a rational psychopharmacological approach.

Promising pharmacologic strategies offering an opportunity for reverse translation

Ketamine: Ketamine, a glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist, was in use in 1970 as an anesthetic but became a drug of abuse due to its dissociative effects (65). It was subsequently observed to relieve depressive symptoms and later demonstrated to be effective for treatment-resistant depression (TRD) (66-68). Recently, its S(+) enantiomer esketamine administered intranasally received FDA approval for TRD in conjunction with an oral antidepressant (69). Ketamine has very rapid effects, acting through glutamatergic signaling as well as secondary brain-derived neurotrophic factor, mammalian targeting of rapamycin (mTOR), and other signaling pathways (70). At the time its antidepressant effects were noted, the potential involvement of the glutamate system in depression was a nascent idea. However, because the drug was already an FDA-approved compound, research could begin prior to a more complete understanding of the drug's neurobiological mechanism(s) of action. Ketamine's actions have led to a greater understanding of the role of glutamatergic function in psychiatric disorders (71).

The initial success of ketamine in TRD trials prompted an interest in ketamine's potential rapid acting effects in PTSD (72-74). A controlled trial using single-dose intravenous ketamine (vs. midazolam) demonstrated rapid reduction in PTSD and depressive symptom severity 24-hours post-infusion (74). Coupled with findings from structural and functional imaging studies, these data have contributed to the hypothesis that PTSD is a "synaptic

disconnection syndrome" (75). Ketamine has been found to increase prefrontal connectivity in depressed patients (76, 77)—a circuit thought to be disrupted in PTSD (78, 79). The initial promising findings for PTSD require replication, and ongoing trials are in progress (73) to determine the duration of potential symptom improvement and maintenance with repeated infusions. If successful, this represents an exciting, contrasting paradigm for drug development, where medications with promise might lead to a greater understanding of disease pathophysiology.

Treatment with rapid-acting medications such as ketamine has prompted the investigation of the role of plasticity in the pathophysiology and treatment of PTSD (75). PTSD-associated synaptic loss, linked to diminished plasticity, has been identified in human post-mortem tissue (80) and suggested by imaging results (reviewed in (75)). Previously discussed mechanisms in PTSD such as changes in GR signaling, inflammatory changes, and alterations in cortisol level also affect synaptic loss, suggesting downstream effects of these disparate systems to a potential final common pathway (75). Therapeutic effects may occur via restoring synaptic connectivity by increasing dendritic spines as evidenced by the observation that ketamine rapidly reversed the synaptic spine deficits caused by chronic stress in the prefrontal cortex in animal studies (81).

A state of induced plasticity, known as "iPlasticity" (82) may allow for environmental stimuli such as rehabilitation to reorganize pathological networks and may be a key factor in resilience. Early data postulates that serotonergic psychedelics, which have been referred to as "psychoplastogens," increase neuritogenesis, spinogenesis, and synaptogenesis to a comparable or greater degree than ketamine (83). The effect is believed to be mediated by engagement of serotonergic-2A receptors (84), and there are many examples to suggest that increasing serotonin levels affects one's sensitivity to the environment (85). An important future direction of treatment may involve catalyzing elements of psychotherapy by creating optimal neural conditions—in this case, perhaps re-opening a critical period of plasticity during which relevant circuits can be engaged and manipulated via targeted psychological rehabilitation (86).

MDMA-Assisted Psychotherapy: MDMA is an amphetamine-derivative belonging to a class of agents known as psychedelics, which promote feelings of euphoria, empathy and trust (87-89). MDMA was first synthesized in 1912, and its ability to catalyze psychotherapy by rapid promotion of introspection and insight in a therapeutic setting was observed anecdotally by the late 1970s (90, 91). MDMA increases release of pre-synaptic serotonin and increases activity at serotonin-2A receptors; is also increases peripheral dopamine (92), cortisol and prolactin (88), and oxytocin (88, 93). Like ketamine, MDMA became popular as a recreational substance ("ecstasy"). Unlike ketamine, MDMA was classified as a Schedule I drug in 1986 and remained that way, effectively blocking investigation into its clinical safety and efficacy for psychiatric conditions until recently (94, 95). MDMA was granted Investigational New Drug status for PTSD in 2004 in the United States after extensive advocacy efforts (95), and was FDA-designated as a "breakthrough therapy" for PTSD in 2017.

Phase-II trials for MDMA-assisted psychotherapy have yielded promising results for PTSD. An initial trial in patients with treatment-resistant PTSD with a mean duration of 20 years demonstrated an effect size of 1.24 and 83% remission rate (96). Long-term follow-up indicated that these responses were durable several years after original dosing (97). The positive and long-term effects were replicated in several other phase II RCTs with remission in treatment-refractory patients varying somewhat by dose, but at its most conservative, 54% (vs. 23% placebo) of patients achieved full remission. Though initial trials with multiple groups in several countries have been promising, the efficacy of MDMA-assisted psychotherapy will depend on the outcome of phase III trials currently underway (98). Similarly to ketamine, effect sizes may also not be comparable to other treatments given that a truly blinded placebo-control condition is difficult given the strong, generally euphoric effects of MDMA; therefore, comparison to a current approved treatment will ultimately prove informative.

Importantly, and unlike ketamine, treatment with MDMA occurs in the context of a psychotherapy protocol where patients receive several preparation sessions prior to two or three full sessions with MDMA, and several integration sessions following each session. The sessions with MDMA last about 8 hours, and are facilitated by two co-therapists who provide psychotherapy as traumatic material is brought forward by the patient. The patient is generally not distressed, but relaxed and introspective. In all, patients receive about 40 hours of psychotherapy with two providers simultaneously, which is twice the length of a course of CBT (98).

Initial concerns were raised about the potential for abuse of a recreational drug and the possibility of use-related cognitive impairment (99-101). However, the study finding dopaminergic neurotoxicity in non-human primates presumed to have been given MDMA was retracted when it was discovered the animals were mistakenly given methamphetamine (102). While safety data are important, there are significant limitations in comparing adverse events in those reporting recreational use vs. those enrolled in a controlled clinical trial. For example, adverse cognitive effects noted in recreational users report lifetime dosages 20-400x that of the cumulative dose used in treatment (103). In contrast, no cognitive impairments were noted in the phase-II trials that featured neuropsychological assessments (98). Safety monitoring and restricted access to medications will need to continue in the early stages of clinical use. The careful psychotherapy protocol in association with MDMA are essential to the actions of this treatment and is absent in recreational use. Nonetheless, it is important to consider the potential for misuse of any medication that has rapid acting effects in improving mood states.

Like ketamine, MDMA-assisted psychotherapy was not designed to engage a target in a mechanistic neural pathway, but its positive effect on patients suffering from PTSD has warranted scientific inquiry into its neural and molecular actions. MDMA may work by creating the optimal neuronal conditions to establish a corrective event as significant as the trauma. A recent pre-clinical study (104) elucidated a potential pathway involving re-opening of the critical period of social learning via oxytocin-dependent induction of long-term depression in the nucleus accumbens, but this needs follow-up study in humans. It has recently been suggested that MDMA assists the psychotherapeutic process by reducing

activation in brain regions implicated in the expression of fear- and anxiety-related behaviors (amygdala and insula), and increasing connectivity between the amygdala and hippocampus. In this manner, MDMA may allow for reprocessing of traumatic memories and emotional engagement with therapeutic processes in an optimized physical and mental state (105). Phenomenologically, MDMA seems to optimize important components of psychotherapy: it reportedly facilitates an optimal level of arousal while processing traumatic memories, increases empathy towards self, catalyzes therapeutic alliance and trust between the patient and the provider and promotes feelings of and desire for connectedness. These factors may allow the patient to engage and process trauma with self-compassion and without feeling overwhelmed (106).

Discussion and Future Considerations

A major purpose of researching the pathophysiology of PTSD is to identify biological dysregulations that might be the proximal cause of symptoms. However, targeting pathways or systems that are altered in PTSD has not led to drastic reductions in PTSD symptoms (e.g. (30, 31, 107)). Rather, among the most promising strategies for PTSD are ketamine and MDMA, compounds that have not emerged from basic research. If they are consistently effective in clinical trials, these strategies will prompt laboratory studies of their mechanism of action that may contribute to a more complete picture of risk and resilience pathways.

The limited success of approaches thus far may reflect that biological findings consistently observed in association with PTSD may not represent key drivers of symptoms, or limitations in methods of observation, including that many biological studies have been performed on blood samples alone, due to the unavailability of brain tissue. A limited number of studies have simultaneously evaluated multiple putative biological pathways (e.g. (108-110)), yet PTSD appears to represent a multi-system, multi-level condition affecting metabolic, neurocognitive, cardiac, immune and brain function. This observation complicates the process of target identification and drug development.

One of the challenges in evaluating the literature on pharmacological strategies is that no single drug has emerged as efficacious for PTSD, though many provide symptom relief in certain patients. It may be that pharmacogenomic strategies may identify PTSD biological subtypes that preferentially respond to specific pharmacologic targets (111, 112). Alternatively biological mechanisms associated with recovery or resilience might be engaged by psychotherapy, and/or facilitated by pharmacological strategies that leverage the strengths of both modalities when used in an integrated manner. Evaluating biological changes before and after such approaches may help understand their mechanisms of action.

Conclusion

The search for druggable targets based on putative pathophysiology, or biological differences between PTSD and resilient persons, has not yet yielded broadly-applicable pharmacological strategies for this disorder. This review has focused on targets drawn from candidate-driven approaches to understanding biological alterations in PTSD, thus, there are still potential targets to be identified using genome-wide systems biology and computational

neuroscience approaches (5). Successful pharmacotherapeutic strategies may depend on identifying biological or clinical subgroups of PTSD, and/or symptom configurations characteristics of specific stages of illness or PTSD phenotypes (113, 114), factors that may not have been fully considered in existing RCTs. Alternatively, approaches to drug development that are borne from understanding the biological correlates of recovery following psychotherapy or pharmacological augmentation of psychotherapy may be needed to identify mechanism associated with successful processing and integration of traumatic material.

The lack of success of strategies based on a one-size-fits-all rational pharmacotherapy justifies a re-evaluation of this approach with the aim of identifying better methods of target detection and more viable compounds or treatments. It is appropriate to learn from promising strategies discovered serendipitously; this can be accomplished using biological psychiatry approaches in reverse translational models to understand the neurobiological mechanisms involved in recovery. Indeed, despite having a clear etiological agent – exposure to an event – PTSD has proven to be an exceedingly heterogeneous and complex condition, and one that is not easily addressed by a single strategy, though often facilitated by combining modalities, including pharmacotherapy and psychotherapy. It is therefore worth considering biological mechanisms that might temporarily alter one's mental state to permit more effective trauma processing. The opportunity to examine the meaning of traumatic life events under the influence of such medications while being guided by skilled psychotherapists may constitute a true personalized medicine strategy for PTSD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Friedman MJ (1988): Toward rational pharmacotherapy for posttraumatic stress disorder: An interim report. The American journal of psychiatry. 145:281–285. [PubMed: 2894174]
2. Friedman MJ (2013): Toward rational pharmacotherapy for posttraumatic stress disorder: reprise. The American Journal of Psychiatry. 170:944–946. [PubMed: 24030605]
3. Feder A, Nestler EJ, Charney DS (2009): Psychobiology and molecular genetics of resilience. Nature Reviews Neuroscience. 10:446–457. [PubMed: 19455174]
4. Horn SR, Feder A (2018): Understanding resilience and preventing and treating PTSD. Harvard review of psychiatry. 26:158–174. [PubMed: 29734229]
5. Neylan TC, Schadt EE, Yehuda R (2014): Biomarkers for combat-related PTSD: focus on molecular networks from high-dimensional data. European journal of psychotraumatology. 5:23938.
6. Russo SJ, Murrough JW, Han M-H, Charney DS, Nestler EJ (2012): Neurobiology of resilience. Nature neuroscience. 15:1475. [PubMed: 23064380]

7. Krystal JH, Davis LL, Neylan TC, Raskind MA, Schnurr PP, Stein MB, et al. (2017): It is time to address the crisis in the pharmacotherapy of posttraumatic stress disorder: a consensus statement of the PTSD Psychopharmacology Working Group. Biological psychiatry. 82:e51–e59. [PubMed: 28454621]
8. Southwick SM, Bonanno GA, Masten AS, Panter-Brick C, Yehuda R (2014): Resilience definitions, theory, and challenges: interdisciplinary perspectives. European journal of psychotraumatology. 5:25338.
9. Harney PA (2007): Resilience processes in context: Contributions and implications of Bronfenbrenner's person-process-context model. Journal of Aggression, Maltreatment & Trauma. 14:73–87.
10. VA/DOD (2017): VA/DOD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder. Washington, DC: Author.
11. ISTSS Guidelines Committee (2018): Posttraumatic Stress Disorder Prevention and Treatment Guidelines: Methodology and Recommendations. International Society for Traumatic Stress Studies (ISTSS).
12. Malejko K, Abler B, Plener PL, Straub J (2017): Neural correlates of psychotherapeutic treatment of post-traumatic stress disorder: A systematic literature review. Frontiers in psychiatry. 8:85. [PubMed: 28579965]
13. VanElzakker MB, Dahlgren MK, Davis FC, Dubois S, Shin LM (2014): From Pavlov to PTSD: the extinction of conditioned fear in rodents, humans, and anxiety disorders. Neurobiology of learning and memory. 113:3–18. [PubMed: 24321650]
14. Abdallah CG, Averill CL, Ramage AE, Averill LA, Alkin E, Nemati S, et al. (2019): Reduced Salience and Enhanced Central Executive Connectivity Following PTSD Treatment. Chronic Stress. 3:2470547019838971.
15. Yehuda R, Hoge CW (2016): The meaning of evidence-based treatments for veterans with posttraumatic stress disorder. JAMA psychiatry. 73:433–434. [PubMed: 26886229]
16. Steenkamp MM (2016): True evidence-based care for posttraumatic stress disorder in military personnel and veterans. JAMA psychiatry. 73:431–432. [PubMed: 26886378]
17. National Institute of Clinical Excellence (2018): Post-traumatic stress disorder. London: NICE.
18. Lee DJ, Schnitzlein CW, Wolf JP, Vythilingam M, Rasmusson AM, Hoge CW (2016): Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: Systemic review and meta-analyses to determine first-line treatments. Depression and anxiety. 33:792–806. [PubMed: 27126398]
19. Pittman R, Orr S (1990): Twenty-four hour urinary cortisol and catecholamine excretion in combat-related posttraumatic stress disorder. Biol Psychiatry. 27:245–247. [PubMed: 2294983]
20. Pitman RK, Orr SP, Forgue DF, de Jong JB, Claiborn JM (1987): Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. Archives of General Psychiatry. 44:970–975. [PubMed: 3675137]
21. Barkay G, Freedman N, Lester H, Louzoun Y, Sapoznikov D, Luckenbaugh D, et al. (2012): Brain activation and heart rate during script-driven traumatic imagery in PTSD: preliminary findings. Psychiatry Research: Neuroimaging. 204:155–160.
22. Krystal JH, Neumeister A (2009): Noradrenergic and serotonergic mechanisms in the neurobiology of posttraumatic stress disorder and resilience. Brain research. 1293:13–23. [PubMed: 19332037]
23. Southwick SM, Krystal JH, Morgan CA, Johnson D, Nagy LM, Nicolaou A, et al. (1993): Abnormal noradrenergic function in posttraumatic stress disorder. Archives of general psychiatry. 50:266–274. [PubMed: 8466387]
24. Hendrickson RC, Raskind MA (2016): Noradrenergic dysregulation in the pathophysiology of PTSD. Experimental neurology. 284:181–195. [PubMed: 27222130]
25. Davis L, Ward C, Rasmusson A, Newell JM, Frazier E, Southwick SM (2008): A placebo-controlled trial of guanfacine for the treatment of posttraumatic stress disorder in veterans. Psychopharmacology bulletin. 41:8–18. [PubMed: 18362867]
26. Neylan TC, Lenoci M, Samuelson KW, Metzler TJ, Henn-Haase C, Hierholzer RW, et al. (2006): No improvement of posttraumatic stress disorder symptoms with guanfacine treatment. American Journal of Psychiatry. 163:2186–2188. [PubMed: 17151174]

27. Berardis DD, Marini S, Serroni N, Iasevoli F, Tomasetti C, de Bartolomeis A, et al. (2015): Targeting the noradrenergic system in posttraumatic stress disorder: a systematic review and meta-analysis of prazosin trials. Current drug targets. 16:1094–1106. [PubMed: 25944011]
28. Singh B, Hughes AJ, Mehta G, Erwin PJ, Parsaik AK (2016): Efficacy of prazosin in posttraumatic stress disorder: a systematic review and meta-analysis. Prim Care Companion CNS Disord. 18.
29. Harpaz-Rotem I, Rosenheck RA (2009): Tracing the flow of knowledge: geographic variability in the diffusion of prazosin use for the treatment of posttraumatic stress disorder nationally in the Department of Veterans Affairs. Archives of General Psychiatry. 66:417–421. [PubMed: 19349311]
30. Raskind MA, Peskind ER, Chow B, Harris C, Davis-Karim A, Holmes HA, et al. (2018): Trial of prazosin for post-traumatic stress disorder in military veterans. New England Journal of Medicine. 378:507–517. [PubMed: 29414272]
31. Argolo FC, Cavalcanti-Ribeiro P, Netto LR, Quarantini LC (2015): Prevention of posttraumatic stress disorder with propranolol: a meta-analytic review. Journal of psychosomatic research. 79:89–93. [PubMed: 25972056]
32. Rodriguez-Romaguera J, Sotres-Bayon F, Mueller D, Quirk GJ (2009): Systemic propranolol acts centrally to reduce conditioned fear in rats without impairing extinction. Biological psychiatry. 65:887–892. [PubMed: 19246030]
33. Friedman MJ, Bernardy NC (2017): Considering future pharmacotherapy for PTSD. Neuroscience letters. 649:181–185. [PubMed: 27890743]
34. Brunet A, Saumier D, Liu A, Streiner DL, Tremblay J, Pitman RK (2018): Reduction of PTSD symptoms with pre-reactivation propranolol therapy: a randomized controlled trial. American Journal of Psychiatry. 175:427–433. [PubMed: 29325446]
35. Tuerk PW, Wangelin BC, Powers MB, Smits JA, Acierno R, Myers US, et al. (2018): Augmenting treatment efficiency in exposure therapy for PTSD: a randomized double-blind placebo-controlled trial of yohimbine HCl. Cognitive behaviour therapy. 47:351–371. [PubMed: 29448886]
36. Yehuda R, LeDoux J (2007): Response variation following trauma: a translational neuroscience approach to understanding PTSD. Neuron. 56:19–32. [PubMed: 17920012]
37. Yehuda R (2018): Neuroendocrinology of PTSD In: Nemeroff CB, Marmar CR, editors. Post-traumatic Stress Disorder. New York: Oxford, pp 353–374.
38. Yehuda R, Halligan SL, Grossman R, Golier JA, Wong C (2002): The cortisol and glucocorticoid receptor response to low dose dexamethasone administration in aging combat veterans and holocaust survivors with and without posttraumatic stress disorder. Biological psychiatry. 52:393–403. [PubMed: 12242055]
39. Duval F, Crocq M-A, Guillon M-S, Mokrani M-C, Monreal J, Bailey P, et al. (2004): Increased adrenocorticotropin suppression following dexamethasone administration in sexually abused adolescents with posttraumatic stress disorder. Psychoneuroendocrinology. 29:1281–1289. [PubMed: 15288707]
40. Yehuda R, Southwick SM, Krystal JH, Bremner D, Charney DS, Mason JW (1993): Enhanced suppression of cortisol following dexamethasone administration in posttraumatic stress disorder. The American Journal of Psychiatry. 150:83–86. [PubMed: 8417586]
41. Yehuda R, Hoge CW, McFarlane AC, Vermetten E, Lanius RA, Nievergelt CM, et al. (2015): Post-traumatic stress disorder. Nature Reviews Disease Primers. 1:15057.
42. Daskalakis NP, McGill MA, Lehrner A, Yehuda R (2016): Endocrine aspects of PTSD: Hypothalamic-Pituitary-Adrenal (HPA) axis and beyond In: Martin CR, Preedy VR, Patel VB, editors. Comprehensive Guide to Post-Traumatic Stress Disorders. Cham, Switzerland: Springer International Publishing, pp 245–260.
43. Yehuda R, Golier J (2009): Is there a rationale for cortisol-based treatments for PTSD? Expert review of neurotherapeutics. 9:1113–1115. [PubMed: 19673600]
44. Schwabe L, Joëls M, Roozendaal B, Wolf OT, Oitzl MS (2012): Stress effects on memory: an update and integration. Neuroscience & Biobehavioral Reviews. 36:1740–1749. [PubMed: 21771612]

45. de Quervain D, Schwabe L, Roozendaal B (2017): Stress, glucocorticoids and memory: implications for treating fear-related disorders. Nature Reviews Neuroscience. 18:7–19. [PubMed: 27881856]
46. Yehuda R (2002): Post-traumatic stress disorder. New England journal of medicine. 346:108–114. [PubMed: 11784878]
47. Golier JA, Yehuda R, Baker D (2017): A randomized clinical trial of a glucocorticoid receptor antagonist in PTSD. Psychoneuroendocrinology. 83:87.
48. Dunlop BW, Binder EB, Iosifescu D, Mathew SJ, Neylan TC, Pape JC, et al. (2017): Corticotropin-releasing factor receptor 1 antagonism is ineffective for women with posttraumatic stress disorder. Biological psychiatry. 82:866–874. [PubMed: 28793974]
49. Schelling G, Stoll C, Kapfhammer H-P, Rothenhäusler H-B, Krauseneck T, Durst K, et al. (1999): The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder and health-related quality of life in survivors. Critical care medicine. 27:2678–2683. [PubMed: 10628609]
50. Schelling G, Roozendaal B, Krauseneck T, Schmoelz M, De Quervain D, Briegel J (2006): Efficacy of hydrocortisone in preventing posttraumatic stress disorder following critical illness and major surgery. Annals of the New York Academy of Sciences. 1071:46–53. [PubMed: 16891561]
51. Zohar J, Yahalom H, Kozlovsky N, Cwikel-Hamzany S, Matar MA, Kaplan Z, et al. (2011): High dose hydrocortisone immediately after trauma may alter the trajectory of PTSD: interplay between clinical and animal studies. European Neuropsychopharmacology. 21:796–809. [PubMed: 21741804]
52. Delahanty DL, Gabert-Quillen C, Ostrowski SA, Nugent NR, Fischer B, Morris A, et al. (2013): The efficacy of initial hydrocortisone administration at preventing posttraumatic distress in adult trauma patients: a randomized trial. CNS spectrums. 18:103–111. [PubMed: 23557627]
53. Amos T, Stein DJ, Ipser JC (2014): Pharmacological interventions for preventing post-traumatic stress disorder (PTSD). Cochrane database of systematic reviews. 7:CD006239–CD006239.
54. Yehuda R, Bierer L, Pratchett L, Malowney M (2010): Glucocorticoid augmentation of prolonged exposure therapy: Rationale and case report. European Journal of Psychotraumatology. 1: 5643.
55. Yehuda R, Bierer LM, Pratchett LC, Lehrner A, Koch EC, Van Manen JA, et al. (2015): Cortisol augmentation of a psychological treatment for warfighters with posttraumatic stress disorder: randomized trial showing improved treatment retention and outcome. Psychoneuroendocrinology. 51:589–597. [PubMed: 25212409]
56. Surís A, North C, Adinoff B, Powell CM, Greene R (2010): Effects of exogenous glucocorticoid on combat-related PTSD symptoms. Annals of Clinical Psychiatry. 22:274–279. [PubMed: 21180658]
57. Maples-Keller JL, Jovanovic T, Dunlop BW, Rauch S, Yasinski C, Michopoulos V, et al. (2019): When translational neuroscience fails in the clinic: Dexamethasone prior to virtual reality exposure therapy increases drop-out rates. Journal of anxiety disorders. 61:89–97. [PubMed: 30502903]
58. Schmeltzer SN, Herman JP, Sah R (2016): Neuropeptide Y (NPY) and posttraumatic stress disorder (PTSD): a translational update. Experimental neurology. 284:196–210. [PubMed: 27377319]
59. Morgan III CA, Wang S, Southwick SM, Rasmusson A, Hazlett G, Hauger RL, et al. (2000): Plasma neuropeptide-Y concentrations in humans exposed to military survival training. Biological psychiatry. 47:902–909. [PubMed: 10807963]
60. Rasmusson AM, Hauger RL, Morgan III CA, Bremner JD, Charney DS, Southwick SM (2000): Low baseline and yohimbine-stimulated plasma neuropeptide Y (NPY) levels in combat-related PTSD. Biological psychiatry. 47:526–539. [PubMed: 10715359]
61. Yehuda R, Brand S, Yang R-K (2006): Plasma neuropeptide Y concentrations in combat exposed veterans: relationship to trauma exposure, recovery from PTSD, and coping. Biological psychiatry. 59:660–663. [PubMed: 16325152]
62. Sah R, Ekhator NN, Strawn JR, Sallee FR, Baker DG, Horn PS, et al. (2009): Low cerebrospinal fluid neuropeptide Y concentrations in posttraumatic stress disorder. Biological psychiatry. 66:705–707. [PubMed: 19576571]
63. Zhou Z, Zhu G, Hariri AR, Enoch M-A, Scott D, Sinha R, et al. (2008): Genetic variation in human NPY expression affects stress response and emotion. Nature. 452:997. [PubMed: 18385673]

64. Sayed S, Van Dam NT, Horn SR, Kautz MM, Parides M, Costi S, et al. (2017): A randomized dose-ranging study of neuropeptide Y in patients with posttraumatic stress disorder. International Journal of Neuropsychopharmacology. 21:3–11.

65. Liu Y, Lin D, Wu B, Zhou W (2016): Ketamine abuse potential and use disorder. Brain research bulletin. 126:68–73. [PubMed: 27261367]

66. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. (2000): Antidepressant effects of ketamine in depressed patients. Biological psychiatry. 47:351–354. [PubMed: 10686270]

67. Zarate CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. (2006): A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Archives of general psychiatry. 63:856–864. [PubMed: 16894061]

68. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, et al. (2013): Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. American Journal of Psychiatry. 170:1134–1142. [PubMed: 23982301]

69. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, et al. (2018): Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. JAMA psychiatry. 75:139–148. [PubMed: 29282469]

70. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, et al. (2013): Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biological psychiatry. 74:250–256. [PubMed: 22840761]

71. Abdallah CG, Sanacora G, Duman RS, Krystal JH (2018): The neurobiology of depression, ketamine and rapid-acting antidepressants: Is it glutamate inhibition or activation? Pharmacology & Therapeutics. 190:148–158. [PubMed: 29803629]

72. Bermudo-Soriano CR, Perez-Rodriguez MM, Vaquero-Lorenzo C, Baca-Garcia E (2012): New perspectives in glutamate and anxiety. Pharmacology Biochemistry and Behavior. 100:752–774.

73. Abdallah CG, Roache JD, Averill LA, Young-McCaughan S, Martini B, Gueorguieva R, et al. (2019): Repeated ketamine infusions for antidepressant-resistant PTSD: Methods of a multicenter, randomized, placebo-controlled clinical trial. Contemp Clin Trials. 81:11–18. [PubMed: 30999057]

74. Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, Saxena S, et al. (2014): Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. JAMA psychiatry. 71:681–688. [PubMed: 24740528]

75. Krystal JH, Abdallah CG, Averill LA, Kelmendi B, Harpaz-Rotem I, Sanacora G, et al. (2017): Synaptic loss and the pathophysiology of PTSD: implications for ketamine as a prototype novel therapeutic. Current psychiatry reports. 19:74. [PubMed: 28844076]

76. Abdallah CG, Averill LA, Collins KA, Geha P, Schwartz J, Averill C, et al. (2017): Ketamine treatment and global brain connectivity in major depression. Neuropsychopharmacology. 42:1210. [PubMed: 27604566]

77. Abdallah CG, Dutta A, Averill CL, McKie S, Akiki TJ, Averill LA, et al. (2018): Ketamine, but not the NMDAR antagonist lanicemine, increases prefrontal global connectivity in depressed patients. Chronic Stress. 2:2470547018796102.

78. Clausen AN, Francisco AJ, Thelen J, Bruce J, Martin LE, McDowd J, et al. (2017): PTSD and cognitive symptoms relate to inhibition-related prefrontal activation and functional connectivity. Depression and anxiety. 34:427–436. [PubMed: 28370684]

79. Stevens JS, Jovanovic T, Fani N, Ely TD, Glover EM, Bradley B, et al. (2013): Disrupted amygdala-prefrontal functional connectivity in civilian women with posttraumatic stress disorder. Journal of psychiatric research. 47:1469–1478. [PubMed: 23827769]

80. Young KA, Thompson PM, Cruz DA, Williamson DE, Selemon LD (2015): BA11 FKBP5 expression levels correlate with dendritic spine density in postmortem PTSD and controls. Neurobiology of stress. 2:67–72. [PubMed: 26844242]

81. Duman RS (2014): Neurobiology of stress, depression, and rapid acting antidepressants: remodeling synaptic connections. Depression and anxiety. 31:291–296. [PubMed: 24616149]

82. Castrén E, Antila H (2017): Neuronal plasticity and neurotrophic factors in drug responses. Molecular Psychiatry. 22:1085–1095. [PubMed: 28397840]

83. Ly C, Greb AC, Cameron LP, Wong JM, Barragan EV, Wilson PC, et al. (2018): Psychedelics promote structural and functional neural plasticity. Cell reports. 23:3170–3182. [PubMed: 29898390]
84. Carhart-Harris RL, Goodwin GM (2017): The therapeutic potential of psychedelic drugs: past, present, and future. Neuropsychopharmacology. 42:2105. [PubMed: 28443617]
85. Branchi I (2011): The double edged sword of neural plasticity: increasing serotonin levels leads to both greater vulnerability to depression and improved capacity to recover. Psychoneuroendocrinology. 36:339–351. [PubMed: 20875703]
86. Nabel EM, Morishita H (2013): Regulating critical period plasticity: insight from the visual system to fear circuitry for therapeutic interventions. Frontiers in psychiatry. 4:146. [PubMed: 24273519]
87. Sessa B (2015): The ecstatic history of MDMA: from raving highs to saving lives. Breaking Convention Book of Proceedings from the 2013 Conference: Strange Attractor Press, pp 87–94.
88. Hysek CM, Schmid Y, Simmler LD, Domes G, Heinrichs M, Eisenegger C, et al. (2013): MDMA enhances emotional empathy and prosocial behavior. Social cognitive and affective neuroscience. 9:1645–1652. [PubMed: 24097374]
89. Wagner MT, Mithoefer MC, Mithoefer AT, MacAulay RK, Jerome L, Yazar-Klosinski B, et al. (2017): Therapeutic effect of increased openness: Investigating mechanism of action in MDMA-assisted psychotherapy. Journal of Psychopharmacology. 31:967–974. [PubMed: 28635375]
90. Grinspoon L, Bakalar JB (1986): Can drugs be used to enhance the psychotherapeutic process? American Journal of Psychotherapy. 40:393–404. [PubMed: 2876654]
91. Stolaroff MJ (2004): The secret chief revealed. Sarasota, Florida: Multidisciplinary Association for Psychedelic Studies.
92. Liechti ME, Vollenweider FX (2001): Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies. Human Psychopharmacology: Clinical and Experimental. 16:589–598. [PubMed: 12404538]
93. Bershad AK, Weafer JJ, Kirkpatrick MG, Wardle MC, Miller MA, de Wit H (2016): Oxytocin receptor gene variation predicts subjective responses to MDMA. Social neuroscience. 11:592–599. [PubMed: 26787430]
94. Sessa B, Nutt DJ (2007): MDMA, politics and medical research: Have we thrown the baby out with the bathwater? : Sage Publications Sage UK: London, England.
95. Heifets BD, Malenka RC (2016): MDMA as a probe and treatment for social behaviors. Cell. 166:269–272. [PubMed: 27419864]
96. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R (2011): The safety and efficacy of ±3, 4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. Journal of Psychopharmacology. 25:439–452. [PubMed: 20643699]
97. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Martin SF, Yazar-Klosinski B, et al. (2013): Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3, 4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. Journal of Psychopharmacology. 27:28–39. [PubMed: 23172889]
98. Mithoefer MC, Feduccia AA, Jerome L, Mithoefer A, Wagner M, Walsh Z, et al. (2019): MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. Psychopharmacology.
99. Parrott AC (2014): MDMA is certainly damaging after 25 years of empirical research: a reply and refutation of Doblin et al.(2014). Human Psychopharmacology: Clinical and Experimental. 29:109–119. [PubMed: 24590542]
100. Murphy PN, Bruno R, Ryland I, Wareing M, Fisk JE, Montgomery C, et al. (2012): The effects of ‘ecstasy’(MDMA) on visuospatial memory performance: findings from a systematic review with meta-analyses. Human Psychopharmacology: Clinical and Experimental. 27:113–138. [PubMed: 22389076]
101. Doblin R, Greer G, Holland J, Jerome L, Mithoefer MC, Sessa B (2014): A reconsideration and response to Parrott AC (2013)“Human psychobiology of MDMA or ‘Ecstasy’: an overview of 25

years of empirical research". Human Psychopharmacology: Clinical and Experimental. 29:105–108. [PubMed: 24590541]

102. Ricaurte GA, Yuan J, Hatzidimitriou G, Cord BJ, McCann UD (2003): Retraction. Science. 301:1479–1479.
103. Multidisciplinary Association for Psychedelic Studies (2017): MDMA Investigational Brochure. MAPS.
104. Nardou R, Lewis EM, Rothhaas R, Xu R, Yang A, Boyden E, et al. (2019): Oxytocin-dependent reopening of a social reward learning critical period with MDMA. Nature. 116–120.
105. Feduccia AA, Mithoefer MC (2018): MDMA-assisted psychotherapy for PTSD: are memory reconsolidation and fear extinction underlying mechanisms? Progress in neuropsychopharmacology and biological psychiatry. 84:221–228.
106. Mithoefer MC, Grob CS, Brewerton TD (2016): Novel psychopharmacological therapies for psychiatric disorders: psilocybin and MDMA. The Lancet Psychiatry. 3:481–488. [PubMed: 27067625]
107. Murrough JW, Charney DS (2017): Corticotropin-Releasing Factor Type 1 Receptor Antagonists for Stress-Related Disorders: Time to Call It Quits? Biological psychiatry. 82:858–860. [PubMed: 29129198]
108. Somvanshi PR, Mellon SH, Flory JD, Abu-Amara D, Wolkowitz OM, Yehuda R, et al. (2018): Mechanistic insights on metabolic dysfunction in PTSD: Role of glucocorticoid receptor sensitivity and energy deficit. bioRxiv 492827.
109. Ratanatharathorn A, Boks MP, Maihofer AX, Aiello AE, Amstadter AB, Ashley-Koch AE, et al. (2017): Epigenome-wide association of Ptsd from heterogeneous cohorts with a common multi-site analysis pipeline. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 174:619–630.
110. Rauch SA, Simon NM, Kim HM, Acierno R, King AP, Norman SB, et al. (2018): Integrating biological treatment mechanisms into randomized clinical trials: Design of PROGrESS (PROlonGed ExpoSure and Sertraline Trial). Contemporary clinical trials. 64:128–138. [PubMed: 29081351]
111. Mushtaq D, Ali A, Margoob MA, Murtaza I, Andrade C (2012): Association between serotonin transporter gene promoter-region polymorphism and 4-and 12-week treatment response to sertraline in posttraumatic stress disorder. Journal of affective disorders. 136:955–962. [PubMed: 21962566]
112. Guo W, Machado-Vieira R, Mathew S, Murrough JW, Charney DS, Gruenbaum M, et al. (2018): Exploratory genome-wide association analysis of response to ketamine and a polygenic analysis of response to scopolamine in depression. Translational Psychiatry. 8:280. [PubMed: 30552317]
113. Galatzer-Levy IR, Bryant RA (2013): 636,120 Ways to Have Posttraumatic Stress Disorder. Perspect Psychol Sci. 8:651–662. [PubMed: 26173229]
114. McFarlane AC, Lawrence-Wood E, Van Hooff M, Malhi GS, Yehuda R (2017): The need to take a staging approach to the biological mechanisms of PTSD and its treatment. Current psychiatry reports. 19:10. [PubMed: 28168596]
115. MacNamara A, Rabinak CA, Kennedy AE, Fitzgerald DA, Liberzon I, Stein MB, et al. (2016): Emotion regulatory brain function and SSRI treatment in PTSD: neural correlates and predictors of change. Neuropsychopharmacology. 41:611. [PubMed: 26111649]
116. Stahl SM (2013): Stahl's essential psychopharmacology: neuroscientific basis and practical applications. Cambridge university press.
117. Tonix Pharmaceuticals Holding Corp (2019): Tonmya for PTSD.
118. Davidson JR, Weisler RH, Butterfield MI, Casat CD, Connor KM, Barnett S, et al. (2003): Mirtazapine vs. placebo in posttraumatic stress disorder: a pilot trial. Biological psychiatry. 53:188–191. [PubMed: 12547477]
119. Alderman CP, Condon JT, Gilbert AL (2009): An open-label study of mirtazapine as treatment for combat-related PTSD. Annals of Pharmacotherapy. 43:1220–1226. [PubMed: 19584388]
120. Averill LA, Purohit P, Averill CL, Boesl MA, Krystal JH, Abdallah CG (2017): Glutamate dysregulation and glutamatergic therapeutics for PTSD: evidence from human studies. Neuroscience letters. 649:147–155. [PubMed: 27916636]

121. Hidalgo R, Hertzberg M, Mellman T, Petty F, Tucker P, Weisler R, et al. (1999): Nefazodone in post-traumatic stress disorder: Results from six open-label trials. International Clinical Psychopharmacology. 14:61–68. [PubMed: 10220119]

122. Difede J, Cukor J, Wyka K, Olden M, Hoffman H, Lee FS, et al. (2014): D-cycloserine augmentation of exposure therapy for post-traumatic stress disorder: a pilot randomized clinical trial. Neuropsychopharmacology. 39:1052–1058. [PubMed: 24217129]

123. de Kleine RA, Hendriks G-J, Kusters WJ, Broekman TG, van Minnen A (2012): A randomized placebo-controlled trial of D-cycloserine to enhance exposure therapy for posttraumatic stress disorder. Biological psychiatry. 71:962–968. [PubMed: 22480663]

124. Rothbaum BO, Price M, Jovanovic T, Norrholm SD, Gerardi M, Dunlop B, et al. (2014): A randomized, double-blind evaluation of D-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan War veterans. American Journal of Psychiatry. 171:640–648. [PubMed: 24743802]

125. Nagele P, Duma A, Kopec M, Gebara MA, Parsoei A, Walker M, et al. (2015): Nitrous oxide for treatment-resistant major depression: a proof-of-concept trial. Biological psychiatry. 78:10–18. [PubMed: 25577164]

126. Grant P, Song JY, Swedo SE (2010): Review of the use of the glutamate antagonist riluzole in psychiatric disorders and a description of recent use in childhood obsessive-compulsive disorder. Journal of child and adolescent psychopharmacology. 20:309–315. [PubMed: 20807069]

127. Locci A, Pinna G (2017): Neurosteroid biosynthesis down-regulation and changes in GABAA receptor subunit composition: a biomarker axis in stress-induced cognitive and emotional impairment. British journal of pharmacology. 174:3226–3241. [PubMed: 28456011]

128. Davidson JR, Brady K, Mellman TA, Stein MB, Pollack MH (2007): The efficacy and tolerability of tiagabine in adult patients with post-traumatic stress disorder. Journal of clinical psychopharmacology. 27:85–88. [PubMed: 17224720]

129. Connor KM, Davidson JR, Weisler RH, Zhang W, Abraham K (2006): Tiagabine for posttraumatic stress disorder: effects of open-label and double-blind discontinuation treatment. Psychopharmacology. 184:21–25. [PubMed: 16341846]

130. Rasmusson AM, Marx CE, Jain S, Farfel GM, Tsai J, Sun X, et al. (2017): A randomized controlled trial of ganaxolone in posttraumatic stress disorder. Psychopharmacology. 234:2245–2257. [PubMed: 28667510]

131. Yehuda R, Brand S, Golier J, Yang RK (2006): Clinical correlates of DHEA associated with post-traumatic stress disorder. Acta Psychiatrica Scandinavica. 114:187–193. [PubMed: 16889589]

132. Boothby LA, Doering PL (2005): Acamprosate for the treatment of alcohol dependence. Clinical therapeutics. 27:695–714. [PubMed: 16117977]

133. Witkiewitz K, Saville K, Hamreus K (2012): Acamprosate for treatment of alcohol dependence: mechanisms, efficacy, and clinical utility. Therapeutics and clinical risk management. 8:45–53. [PubMed: 22346357]

134. Horrigan JP (1996): Guanfacine for PTSD nightmares. Journal of the American Academy of Child and Adolescent Psychiatry. 35:975–976.

135. Harmon RJ, Riggs PD (1996): Clonidine for posttraumatic stress disorder in preschool children. Journal of the American Academy of Child & Adolescent Psychiatry. 35:1247–1249. [PubMed: 8824068]

136. Connor DF, Grasso DJ, Slivinsky MD, Pearson GS, Banga A (2013): An open-label study of guanfacine extended release for traumatic stress related symptoms in children and adolescents. Journal of child and adolescent psychopharmacology. 23:244–251. [PubMed: 23683139]

137. Graham DP, Nielsen DA, Kosten TR, Davis LL, Hamner MB, Makotkine I, et al. (2014): Examining the Utility of Using Genotype and Functional Biology in a Clinical Pharmacology Trial: Pilot Testing Dopamine β-Hydroxylase, Norepinephrine, and PTSD. Psychiatric genetics. 24:181–182. [PubMed: 24983834]

138. Golier JA, Caramanica K, DeMaria R, Yehuda R (2012): A pilot study of mifepristone in combat-related PTSD. Depression Research and Treatment. 2012:393251. [PubMed: 22611490]

139. Golier JA, Caramanica K, Michaelides AC, Makotkine I, Schmeidler J, Harvey PD, et al. (2016): A randomized, double-blind, placebo-controlled, crossover trial of mifepristone in Gulf War

veterans with chronic multisymptom illness. Psychoneuroendocrinology. 64:22–30. [PubMed: 26600007]

140. Bitencourt RM, Takahashi RN (2018): Cannabidiol as a Therapeutic alternative for post-traumatic stress disorder: from bench research to confirmation in human trials. Frontiers in neuroscience. 12.
141. Pietrzak RH, Naganawa M, Huang Y, Corsi-Travali S, Zheng M-Q, Stein MB, et al. (2014): Association of in vivo κ-opioid receptor availability and the transdiagnostic dimensional expression of trauma-related psychopathology. JAMA psychiatry. 71:1262–1270. [PubMed: 25229257]
142. Lake EP, Mitchell BG, Shorter DI, Kosten T, Domingo CB, Walder AM (2019): Buprenorphine for the treatment of posttraumatic stress disorder. The American journal on addictions. 28:86–91. [PubMed: 30664299]
143. Zoellner LA, Telch M, Foa EB, Farach FJ, McLean CP, Gallop R, et al. (2017): Enhancing extinction learning in posttraumatic stress disorder with brief daily imaginal exposure and methylene blue: a randomized controlled trial. The Journal of clinical psychiatry. 78:e782–e789. [PubMed: 28686823]
144. Lee RJ, Coccaro EF, Cremers H, McCarron R, Lu S-F, Brownstein M, et al. (2013): A novel V1a receptor antagonist blocks vasopressin-induced changes in the CNS response to emotional stimuli: an fMRI study. Frontiers in systems neuroscience. 7:100. [PubMed: 24376401]
145. Donadon MF, Martin-Santos R, Osório FdL (2018): The associations between oxytocin and trauma in humans: a systematic review. Frontiers in pharmacology. 9:154. [PubMed: 29545749]
146. Mathew SJ, Vythilingam M, Murrough JW, Zarate CA Jr, Feder A, Luckenbaugh DA, et al. (2011): A selective neurokinin-1 receptor antagonist in chronic PTSD: a randomized, double-blind, placebo-controlled, proof-of-concept trial. European Neuropsychopharmacology. 21:221–229. [PubMed: 21194898]
147. Garakani A, Murrough JW, Iosifescu DV (2014): Advances in psychopharmacology for anxiety disorders. Focus. 12:152–162.
148. Surís A, Smith J, Powell C, North CS (2013): Interfering with the reconsolidation of traumatic memory: sirolimus as a novel agent for treating veterans with posttraumatic stress disorder. Annals of Clinical Psychiatry. 25:33–40. [PubMed: 23376868]

Table 1.

Candidate PTSD pharmacotherapies

Target System	Target Engagement	Rationale for use in PTSD
Monoaminergic	SSRIs, TCAs, MAOIs, Nefazadone, Venlafaxine, Trazodone, antipsychotics,mirtazapine, bupropion, TNX-102 (115-121)	Treatment of symptoms overlapping with depression; perhaps PTSD involves diminished capacity to downregulate 5-HT1B receptors; alterations of serotonergic receptors in the amygdala; connection of serotonin, trauma, and hippocampal volume
Glutamatergic	D-cycloserine, Pregabalin, Ketamine, Riluzole, Nitrous Oxide, SNC-102 (73, 74, 122-126)	Glutamatergic pathway in PTSD still under investigation, but likely related to the effect of chronic stress on learning and memory; ketamine may rapidly promote neuroplasticity in PTSD
GABAergic	Benzodiazepines, pregnenolone, tiagabine, Ganaxolone, Topiramate, Riluzole, 7-Keto DHEA, SNC-102 (126-133)	Symptomatic improvement of anxiety; Possible PTSD deficits in GABA signaling
Adrenergic	Clonidine, Guanfacine, Prazosin, propranolol, Yohimbine, Nepicastat, Doxazosin, 7-Keto DHEA (28, 30, 34, 131, 134-137)	Central and peripheral adrenergic hypersensitivity and hyperactivity
HPA Axis	Hydrocortisone, Mifepristone, GSK561679, Neuropeptide Y, 7-Keto DHEA, SRX246 (49-52, 58, 131, 138, 139)	Major constituent of the neuroendocrine response to acute and chronic stress
Endocannabinoid	CB1 agonists, Cannabidiol (140)	Reduction of hyperadrenergic activity with the specific intent of blocking reconsolidation of fear memory; possible prophylactic immediately after trauma
Opiate	buprenex/vivitrol (141, 142)	Observation that patients self-medicate with opioids to alleviate symptoms of hypervigilance and hyperarousal; preclinical data demonstrating improved behavioral responses to stress
Unknown mechanism	Gabapentin	Often for comorbid/overlapping symptom reduction
Mitochondrial respiration in nerve cells	methylene blue (143)	Enhance extinction learning
Oxytocin-related and Vasopressinergic	SRX246 and oxytocin (144, 145)	Preclinical and preliminary clinical data suggesting these agents may correct a dysregulation of vasopressin and oxytocin signaling in stress-related illnesses
Substance P/tachykinin pathway	Orvepitant, Neurokinin 1 antagonists, GR205171 (146)	Substance P-neurokinin1 involved in experimental models of stress, fear, reward; substance P elevated in PTSD CSF
Nicotinic	BNC210 (147)	Anxiolytic without cognitive or sedating effects of benzodiazepines
Protein Synthesis	Sirolimus (148)	Inhibit mTOR to alter amygdala and hippocampal dendritic arborization during exposure to modify reconsolidation of traumatic memory
Optimizing psychotherapy	MDMA, hydrocortisone, D-cycloserine, yohimbine (35, 122-124)	Psychotherapy is the most effective treatment so perhaps medications can make the therapy more accessible and the effects more robust and long-lasting