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Review

Translating Molecular and Neuroendocrine Findings in Posttraumatic Stress Disorder 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 article 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, hypothalamic-pituitary-adrenal axis, and neuropeptide Y systems. Other highlighted approaches involve the use of ketamine and 3,4-methylenedioxymethamphetamine–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 posttraumatic symptoms. To the extent that use of ketamine and 3,4-methylenedioxymethamphetamine promotes symptom improvement and resilience in PTSD, this provides an opportunity for reverse translation and identification of relevant targets and mechanisms 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.

Keywords: Glucocorticoids, Ketamine, MDMA, Pharmacotherapy, PTSD, Resilience

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Shortly after the appearance of posttraumatic stress disorder (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 (1) was made when little was known about the biology of PTSD, but many believed that 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 posttraumatic 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/reintegrative processes of healing accomplished via successful treatment (8,9).

Currently approved medications for PTSD are limited to selective serotonin reuptake inhibitors, 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

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 is 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 that 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/neurokinin 1 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

5-HT1B, 5-hydroxytryptamine receptor 1B; CB1, cannabinoid receptor type 1; CSF, cerebrospinal fluid; DHEA, dehydroepiandrosterone; GABA, gamma-aminobutyric acid; HPA, hypothalamic-pituitary-adrenal; MAOI, monoamine oxidase inhibitor; MDMA, 3,4-methylenedioxymethamphetamine; mTOR, mammalian target of rapamycin; PTSD, posttraumatic stress disorder; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant.

patients. Traumatic exposures result in not only behavioral symptoms, but also a disruption of the survivor's worldviews, 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 catalyzed, 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 because the patient does not want, failed to respond to, dropped out of, 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 α_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 α_2 agonists clonidine and guanfacine, have met limited success (25,26). An exception is the α_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 the Department of Veterans Affairs and in 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 1-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 corticotropin-releasing hormone 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 corticotropin-releasing hormone 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). As catecholamines facilitate the consolidation of memories (44) and cortisol facilitates extinction and interferes with fear memory reconsolidation (45), suboptimal levels of cortisol in the presence 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 long-term administration of steroids in nonendocrine 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 multisite phase II randomized clinical trial of the GR antagonist mifepristone comprising a 600-mg daily dose for 1 week indicated no overall advantage over placebo for PTSD symptoms (47). Subgroup analysis indicated that combat veterans without a history of mild traumatic brain injury experienced significant symptom improvements with mifepristone. Dunlop *et al.* (48) showed no improvement in PTSD in a placebo-controlled trial of a corticotropin-releasing hormone 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 current preventive pharmacological agent with a convincing evidence base. 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, a cognitive behavioral therapy. An initial case report found greater improvement in PTSD symptoms postexposure 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 1 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 dropout 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 Schmeltzer *et al.* (58)]. NPY, a neuropeptide implicated in anxiety-related behavior, regulates HPA axis activity by stimulating release of adrenocorticotropic hormone 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, who are considered to be 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 PTSD, compared with those who never had it (61). Veterans with chronic PTSD were also found to have lower concentrations of cerebrospinal fluid NPY relative to healthy control subjects (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 crossover 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 receptor antagonist, was in use in 1970 as an anesthetic but became a drug of abuse owing to its dissociative effects (65). It was subsequently observed to relieve depressive symptoms and later demonstrated to be effective for treatment-resistant depression (66–68). Recently, its S(+) enantiomer esketamine administered intranasally received Food and Drug Administration approval for treatment-resistant depression 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 target of rapamycin, 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 a Food and Drug Administration–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 treatment-resistant depression 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 at 24 hours postinfusion (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, in which 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 postmortem tissue (80) and suggested by imaging results [reviewed in Krystal *et al.* (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 reopening a critical period of plasticity during which relevant circuits can be engaged and manipulated via targeted psychological rehabilitation (86).

3,4-Methylenedioxymethamphetamine–Assisted Psychotherapy. 3,4-Methylenedioxymethamphetamine (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 presynaptic 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 designated by the Food and Drug Administration 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 randomized clinical trials, 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). Similar 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 in which patients receive several preparation sessions prior to 2 or 3 full sessions with MDMA, and several integration sessions following each session. The sessions with MDMA last about 8 hours and are facilitated by 2 co-therapists who provide psychotherapy as traumatic material is brought forward by the patient. The patient is generally not distressed, but rather is relaxed and introspective. In all, patients receive about 40 hours of psychotherapy with 2 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 nonhuman primates presumed to have been given MDMA was retracted when it was discovered that 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 versus those enrolled in a controlled clinical trial. For example, adverse cognitive effects noted in recreational users report lifetime dosages 20× to 400× 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 rather 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 preclinical study (104) elucidated a potential pathway involving reopening 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 toward 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, owing 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 multisystem, multilevel 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.

CONCLUSIONS

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 configuration characteristics of specific stages of illness or PTSD phenotypes (113,114), factors that may not have been fully considered in existing randomized clinical trials. 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 treatment is often facilitated by combining modalities, including pharmacotherapy and psychotherapy. Therefore, it is 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.

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AF is named co-inventor on a patent application in the United States, and several issued patents outside the U.S. filed by the Icahn School of Medicine at Mount Sinai related to the use of ketamine for the treatment of posttraumatic stress disorder. This intellectual property has not been licensed. RY is listed as co-inventor on a U.S. patent pertaining to genetic testing in posttraumatic stress disorder. All other authors report no biomedical financial interests or potential conflicts of interest.

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