Biological Psychiatry

It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group

To the Editor:

There is an urgent need to address a critical lack of advancement in the psychopharmacologic treatment of posttraumatic stress disorder (PTSD). The clinical, social, and financial burden of ineffectively treated PTSD is enormous (1–6). The impact of PTSD morbidity and mortality is further magnified by its substantial disruptions in family, workplace, and societal contexts (7). For the Department of Veterans Affairs (VA) and Department of Defense (DoD), i.e., institutions that are vehicles for the expression of the national debt to military personnel who developed PTSD as a consequence of their military service, the need to help these people has taken on significant priority. One in 10 VA healthcare users have the diagnosis of PTSD, which includes one in four treatment-seeking veterans of the recent wars in Iraq and Afghanistan (8). The prevalence of PTSD in the general population for lifetime is approximately 8% (8) and just under 4% for the current year, making it the fifth most prevalent mental disorder in the United States (9–11). Despite this high prevalence and costly impact, there seems to be no visible horizon for advancements in medications that treat symptoms or enhance outcomes in persons with a diagnosis of PTSD.

The nature of this PTSD pharmacotherapy crisis is threefold. First, there are only two medications currently approved for the treatment of PTSD by the U.S. Food and Drug Administration (FDA), sertraline (Zoloft) and paroxetine (Paxil). These medications are helpful but are believed to work via the same mechanism of action (12), and both produce reduction in symptom severity rather than remission of PTSD symptoms (13,14). This efficacy gap may be particularly great for patients treated in VA settings (13). Second, the limited efficacy of the FDA-approved treatments for PTSD has necessitated polypharmacy for the vast majority of patients treated. These off-label medications, as monotherapy or in combination with other medications, have not been studied adequately for the treatment of PTSD. Therefore, most patients are treated with medications or combinations for which there is little empirical guidance regarding benefits and risks. Third, research and development of new medications for the treatment of PTSD has stalled and there is a void in new drug development. There has not been a medication approved for the treatment of PTSD since 2001, despite the significant need. In a survey of ClinicalTrials.gov, there were few pharmaceutical industry-sponsored clinical trials for PTSD that have enrolled patients since 2006: one Phase III clinical trial, four Phase II clinical trials, and no Phase I clinical trials (see The Limited Research Portfolio, below). There is no doubt that there is a deficient pipeline of new PTSD medications and it is uncertain about how to best identify new targets for medication development. Even if there were a more robust investment in PTSD research, questions would remain regarding the optimal design for these studies. The past decade of investments from VA and other federal funding agencies in research on medical treatment of military personnel and veterans with PTSD have yet to bear fruit in the form of new validated pharmacotherapies for PTSD.

Paradoxically, this is a time of tremendous progress in the basic neuroscience of stress and PTSD that could inform the identification of novel therapeutic targets (14,15). There is a longstanding translational neuroscience tradition in PTSD research (16,17). However, recent developments in the genetics and epigenetics of PTSD (18–20), progress with animal models (21), the emergence of the first molecular analyses of postmortem brain tissue from people with PTSD (22), an expanding number of brain molecular targets probed with positron emission tomography imaging (23), the refinement of the neural circuitry of PTSD through structural (24) and functional (25) brain imaging, and the refinement of behavioral paradigms to study many relevant dimensions of the PTSD syndrome, partly in the context of the National Institute of Mental Health (NIMH) Research Domain Criteria initiative, all contribute to the readiness of the field to test novel PTSD therapeutics. Further, the advances in neuroscience provide a foundation for the rational combinations of new medications with novel cognitive and behavioral therapies (26).

In June 2016, the VA Office of Research and Development convened an internal PTSD Psychopharmacology Working Group to evaluate potential directions in PTSD psychopharmacology research. The Working Group reviewed the status of the current pharmacotherapy options and new research focused on PTSD drug development. This review spanned early phase to definitive clinical trials. The group identified only a very small portfolio of VA research aimed at advancing the pharmacotherapy of PTSD. In the following sections, we will review the knowledge gap related to the pharmacotherapy for PTSD, the current limited research portfolio of PTSD pharmacotherapy research, a case study of the evaluation of a novel early phase therapeutic agent, some emerging research targets, and conclusions of the Working Group.

Overall, the PTSD Psychopharmacology Working Group concluded that the current PTSD pharmacotherapy research effort was not adequate in terms of the number of investigators, medications of interest, and stages of research to address the urgent needs across a larger clinical community for improving PTSD treatment. The consensus of the Work Group was that renewed and concerted efforts in three critical areas were needed to advance science and treatment outcomes: 1) foundational efficacy and effectiveness studies of medications already widely prescribed for the treatment of PTSD; 2) early phase trials of novel pharmacologic agents with greater partnership between the pharmaceutical industry, government agencies, and academic investigators; and (3) investment in the development of a workforce and infrastructure capable of conducting the needed research. The basis for these conclusions is presented in the following report.

The Knowledge Gap

The field of PTSD pharmacotherapy research lags behind that of most other serious mental illnesses in terms of its history

SEE COMMENTARY ON PAGE 460

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and depth. The first randomized placebo-controlled trial (RCT) in PTSD was conducted relatively recently, in 1988 (27). This small study suggested the efficacy of a monoamine oxidase inhibitor and a tricyclic antidepressant in combat veterans with PTSD. Although there are now two FDA-approved serotonin reuptake inhibiting (SRI) antidepressants, sertraline (28,29) and paroxetine (30,31), there have been few additional large multicenter pharmacotherapy studies for PTSD. The small number of informative RCTs in PTSD and the lack of head-to-head comparison studies contributes to the conclusion, based on meta-analysis, that pharmacotherapies are less effective than trauma-focused psychotherapies for the treatment of PTSD (32) and the Institute of Medicine conclusion that there are insufficient evidence on the efficacy of pharmacotherapies for the treatment of PTSD (33).

The limited evidence base for the pharmacotherapy of PTSD is a major obstacle to the effective treatment of this disorder. Of particular concern to the VA and the DoD is that the established medications, SRIs, may have limited efficacy for male patients. For example, while showing effectiveness in the overall study population, sertraline was not more effective than placebo in the subgroup of male patients, predominately veterans, in one multicenter trial (28). Also, a sertraline study conducted entirely within combat veterans failed to demonstrate efficacy (13). Based on a review of VA Pharmacy records from fiscal year 2015, 70% of VA patients with a diagnosis of PTSD were prescribed an antidepressant (34), and the SRIs are the most commonly prescribed antidepressant for the treatment of PTSD (35).

Beyond antidepressants, no medication that is commonly prescribed for the treatment of veteran patients with PTSD meets multisite Phase III standards of validation to support their widespread prescription. Yet the limited efficacy of SRIs and the clinical severity of PTSD symptoms leads clinicians to attempt to prescribe medications that have inadequate or even absent empirical validation for the treatment of PTSD. For example, symptomatic patients recruited from 23 VA Medical Centers for a treatment study for antidepressant-resistant PTSD symptoms of PTSD were treated with approximately three medications prior to starting their fourth "research" medication, a sign that available medications are often ineffective in usual clinical practice (36).

Table 1 indicates that, in addition to antidepressants, the medication classes most commonly prescribed to VA patients with PTSD include anticonvulsants, second-generation antipsychotics, sedative hypnotics, and opioids (37). Trazodone is the most frequently prescribed antidepressant for PTSD, and there has been a steady year-by-year increase in prazosin use to 25.8% in 2013 (37,38). Both of these medications are prescribed principally to treat sleep-related symptoms in PTSD. The dissemination of trazodone and prazosin prescribing probably emerged from the prominence of sleep-related symptoms, the desire of clinicians to avoid prescribing addictive medications, favorable clinical experience of individual clinicians, regional patterns of practice (39), preliminary evidence of efficacy in published reports of pilot studies (40,41), and hypotheses regarding their ability to correct abnormalities in neural signaling associated with PTSD (42). Exemplars of two of these frequently prescribed medication classes, second-generation antipsychotics (risperidone) and anticonvulsants (tiagabine), failed to show efficacy in multicenter trials (36,43). Most recently, a multicenter clinical trial evaluating prazosin, supported by the VA Cooperative Studies Program, has posted results on ClinicalTrials.gov, suggesting a lack of efficacy (NCT00532493). Furthermore, benzodiazepines, historically one of the medications most commonly prescribed in patients with PTSD, failed to show efficacy in small pilot studies (44,45) and interfered with fear extinction in another study (46); although one study with a hypnotic drug (eszopiclone) was positive (47). Benzodiazepine prescription declined by approximately 6% from 1999 to 2009 (48) but appears to have stabilized thereafter (37). In addition, the possibility that benzodiazepine prescription would worsen PTSD symptoms or increase substance abuse risk (49) in substance abusers does not appear to be supported by a retrospective analysis (50). This analysis also suggested that benzodiazepine prescription might reduce service utilization among veterans with PTSD (50). Thus, the safety and efficacy of benzodiazepines and related agents remains unclear despite the long history and high rate of prescription of these drugs to veterans with PTSD. The insufficient evidence of efficacy of commonly prescribed medications leaves physicians without clear guidelines as how to effectively treat veterans with PTSD or to empirically appraise and manage risk/benefit issues.

The recent inability to demonstrate efficacy of risperidone and prazosin in relatively large VA clinical trials has raised several questions ranging from the adequacy of animal models to inform the selection of effective drug targets to critical elements of study design. Questions for the field include the following: 1) How can we identify new mechanisms of action that have a high probability of efficacy in treating PTSD? 2) Do we need new types of study designs (i.e., medications added to treatment as usual vs. specific psychosocial treatments) or outcomes (i.e., global vs. specific outcomes)? 3) Should we target specific subpopulations of patients as opposed to the total pool of PTSD patients? 4) Have our exclusion criteria in previous trials (e.g., psychiatric instability) excluded subjects who are more acutely ill and perhaps more likely to respond to pharmacotherapy? and 5) How should medications be combined for optimal PTSD treatment? These questions cross the boundaries of diagnosis-based research and the dimensional perspective represented by the NIMH Research Domain Criteria. Furthermore, they point toward the objective of delivering personalized PTSD treatment. In addition, multicenter pharmacotherapy studies of PTSD in veterans conducted by the VA Cooperative Studies Program, i.e., VA Cooperative Studies Program #504 (risperidone) (36) and VA Cooperative Studies Program #563 (prazosin) enrolled more than 95% male patients. The underrepresentation of female veterans in PTSD pharmacotherapy research could limit the applicability of VA pharmacotherapy research findings to this population, leaving little guidance related to sex differences in PTSD pharmacotherapy (51).

Historically, the Clinician-Administered PTSD Scale total score (52) has been the primary outcome measure for definitive clinical trials, typical for Phase III of the FDA approval process. However, it is increasingly recognized that some medications that might be helpful for PTSD may preferentially affect only some symptom clusters or psychophysiologic characteristics. For example, risperidone may be helpful for

Table 1. Medications Filled as Prescriptions in the Year Following Initial PTSD Diagnosis, 2004–2013

	Fiscal Year				
	2004	2007	2010	2013	Overall
New PTSD Episodes	51,750	69,604	84,850	82,546	731,520
Mean Number of Psychotropics	3.5 ± 2.5	3.5 ± 2.6	3.6 ± 2.7	3.5 ± 2.7	3.5 ± 2.7
All Antidepressants	85.1 (44,026)	82.7 (57,544)	80.1 (68,001)	78.0 (64,394)	81.0 (592,505)
Amitriptyline	5.7 (2948)	4.6 (3195)	3.8 (3221)	3.7 (3074)	4.2 (31,019)
Mirtazapine	12.4 (6392)	12.3 (8578)	12.9 (10,973)	13.0 (10,722)	12.6 (92,460)
Nefazodone	1.2 (638)	0.3 (237)	0.1 (116)	0.1 (50)	0.3 (2097)
Phenelzine	0.0 (20)	0.0 (10)	0.0 (8)	0.0 (8)	0.0 (92)
Trazodone	33.4 (17,296)	32.3 (22,484)	30.5 (25,847)	29.7 (24,489)	31.0 (226,812)
Any SSRI or SNRI	70.1 (36,290)	67.6 (47,064)	65.7 (55,740)	63.1 (52,112)	66.3 (485,194)
Fluoxetine	13.9 (7212)	11.8 (8246)	9.5 (8022)	11.5 (9481)	11.3 (82,346)
Paroxetine	10.3 (5331)	7.0 (4842)	5.0 (4266)	6.0 (4951)	6.6 (48,215)
Sertraline	26.0 (13,449)	16.3 (11,367)	21.4 (18,145)	31.2 (25,771)	22.9 (167,613)
Venlafaxine	9.2 (4770)	8.5 (5882)	8.4 (7121)	11.7 (9680)	9.1 (66,747)
All Anticonvulsants	21.8 (11,267)	22.8 (15,871)	26.0 (22,080)	29.1 (24,005)	24.9 (182,077)
Gabapentin	11.1 (5739)	12.1 (8399)	15.2 (12,851)	18.2 (15,001)	14.1 (102,791)
Topiramate	2.1 (1072)	2.6 (1832)	3.3 (2764)	4.3 (3517)	3.1 (22,803)
Valproic acid	7.3 (3794)	6.8 (4723)	6.8 (5732)	6.2 (5152)	6.7 (49,197)
Prazosin	6.1 (3171)	9.6 (6690)	17.3 (14,641)	25.8 (21,291)	15.0 (110,048)
All Atypical Antipsychotics	29.7 (15,390)	23.8 (16,562)	20.3 (17,185)	16.9 (13,944)	21.8 (159,757)
Olanzapine	4.5 (2347)	1.9 (1342)	1.7 (1444)	1.6 (1298)	2.0 (14,691)
Quetiapine	18.9 (9758)	15.8 (10,970)	11.5 (9728)	9.0 (7426)	13.3 (97,542)
Risperidone	9.9 (5126)	6.1 (4248)	5.1 (4323)	4.7 (3917)	5.8 (42,311)
All Typical Antipsychotics	1.8 (946)	1.8 (1275)	1.8 (1526)	1.8 (1485)	1.8 (13,304)
All Addiction Medicines[a]	7.8 (4027)	12.4 (8665)	12.9 (10,984)	12.9 (10,637)	11.9 (87,361)
All Sedative Hypnotics	38.2 (19,776)	37.9 (26,353)	41.3 (35,085)	35.4 (29,262)	38.9 (284,877)
Zolpidem	4.6 (2404)	7.9 (5532)	18.2 (15,472)	14.3 (11,837)	13.0 (95,086)
Any benzodiazepine	34.9 (18,066)	32.9 (22,907)	29.4 (24,979)	25.1 (20,756)	30.3 (221,309)
All Opioids[b]	35.4 (18,325)	37.8 (26,301)	38.3 (32,473)	34.6 (28,564)	36.9 (270,103)
All Stimulants	1.1 (592)	1.5 (1060)	2.3 (1991)	3.3 (2702)	2.1 (15,690)
Lithium	1.8 (942)	1.4 (951)	1.4 (1162)	1.5 (1254)	1.4 (10,580)
Buspirone	5.1 (2665)	4.7 (3241)	4.9 (4168)	6.4 (5269)	5.1 (37,614)

Values are mean ± SD or % (n). Data from Shiner and Westgate (37). Cohort is described in detail elsewhere (38).
PTSD, posttraumatic stress disorder; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.
[a]Includes acamprosate, buprenorphine, disulfuram, naltrexone, nicotine replacement, and varenicline.
[b]Includes all opioids in this class code (excluding methadone from methadone clinic) plus tramadol.

insomnia associated with PTSD (39). Additionally, prazosin has been found to be particularly helpful for insomnia and nightmares associated with PTSD (53–55) and showed significant efficacy in patients with greater than average baseline standing systolic blood pressure, a potential sign of noradrenergic activation, but its efficacy was no better than placebo in patients with lower than average standing systolic blood pressure (56).

Ultimately, PTSD pharmacotherapy research should guide clinical practice. For nearly every psychiatric disorder, it is common to distinguish between strategies applied to "first-line" treatments for unselected patients early in their course of illness and treatment approaches for more severe symptoms or symptoms that have not responded to first-line treatments, so-called treatment-resistant illness. Although treatment algorithms staging treatments have been proposed (57,58), none of these algorithms have a sufficient evidence base to be reliable. The gap in the evidence base for the management of SRI-resistant PTSD symptoms is even more severe than the gap related to PTSD treatment as a whole. The notion of treatment-resistant PTSD needs to take its place alongside treatment-resistant depression, bipolar disorder, or schizophrenia guiding the development and validation of treatment approaches for these patients.

The Limited Research Portfolio

Gaps in the efficacy of pharmacotherapies for PTSD do not appear to be triggering a surge in research and development. The fact that veterans with PTSD are typically treated with medication combinations that have little, if any, empirical support by RCTs should evoke a flood of research aimed at addressing this critical information gap There has not been a commensurate increase in the number of independent PTSD psychopharmacology project grants by federal funding agencies. A search of National Institutes of Health eRePorter on December 5, 2016, for VA and NIMH PTSD medication trials

Table 2. Phase II Industry-Sponsored Drug Clinical Trials for PTSD in the United States Since 2006

Study Name	Intervention	Status	Industry Sponsor	Results
Orvepitant (GW823296) in Adult Posttraumatic Stress Disorder	Orvepitant vs. placebo	Completed (2/2012)	GlaxoSmithKline	Early study termination and small sample size precluded making any definitive efficacy conclusions (63).
7-Keto DHEA for the Treatment of PTSD	7-Ketodehydroepiandrosterone vs. placebo	Completed (2/2014)	Humanetics Corporation	No published results
Safety & Efficacy Study of TNX-102 SL in Subjects With Military-Related PTSD & Related Conditions	TNX 102-SL (5.6 mg) vs. TNX-102-SL (2.8 mg) Placebo	Completed (5/2016)	Tonix Pharmaceuticals	This study identified the 5.6-mg dose as clinically effective and well tolerated dose for registration trials. The 2.8-mg dose trended in direction of therapeutic effect, but did not reach statistical significance on primary endpoint (64).
Open Label Extension Safety & Efficacy Study of TNX-102 SL Tablets in Military Related PTSD & Related Conditions	TNX-102 SL (cyclobenzaprine)	Completed (7/2016)	Tonix Pharmaceuticals	Primary safety results. The 2.8-mg dose was not statistically significant as compared with placebo. (This study assumed 2.8-mg dose would be effective, so all participants were switched to or continued on 2.8-mg dose).[a]

[a]G. Sullivan, M.D., personal communication, Feb 17, 2017.

currently funded identified VA supporting only two studies involving pharmacotherapy intervention in fiscal year 2016. Neither of these studies tested novel agents developed for PTSD, i.e., they were studying medications that had FDA approval for the treatment of other psychiatric disorders. NIMH data show that of the 21 active grants supporting human PTSD research, three were supporting the evaluation of pharmacotherapies for PTSD.

There are many potential reasons for the limited PTSD psychopharmacology research. Few PTSD psychopharmacology experts are submitting clinical trial applications. Testing of widely prescribed but unvalidated medications may not stimulate studies because these grants might be perceived as being of limited novelty. There may be inadequate data on pharmacodynamic and pharmacokinetic properties, such as dose-related brain target engagement, that might inform optimal drug dosing in clinical trials. In addition, researchers may perceive that it would be difficult to create partnerships between funding agencies and the pharmaceutical industry to support novel RCTs because of concerns pertaining to intellectual property. Regardless, the need for federal, industry, scientific, and clinical communities to cooperatively address the state of affairs cannot be ignored.

Given concerns related to the degree of efficacy of the SRIs and the absence of validated alternatives, the limited investment in PTSD research by the pharmaceutical industry has particularly serious implications for addressing the needs of affected individuals and society in general. Over the past 10 years, according to a search of ClinicalTrials.gov, the pharmaceutical industry has completed four Phase II clinical trials and one Phase III clinical trial testing the efficacy of new agents for the treatment of PTSD in the United States. The drugs and sponsors are summarized in Tables 2 and 3.

In addition, through a search of ClinicalTrials.gov, there have been 13 investigator-initiated Phase II clinical trials in the United States, conducted by academic investigators in collaboration with pharmaceutical companies who made the drugs available and/or another federal agency. As presented in Table 4, these studies were conducted with support from VA, DoD, and other federally funded agencies. In each of these cases, a drug that failed to demonstrate efficacy for its primary indication was repurposed for PTSD. Three phase III clinical trials are presented in Table 5. One of the three studies (trial 3) published negative results (59), one study (trial 2) listed negative results on ClinicalTrials.gov (NCT00532493), and one study (trial 1) had no results posted on ClinicalTrials.gov (NCT00413296). When results were not posted on ClinicalTrials.gov, a more extensive search on PubMed Central and/or trying to contact the investigators was performed to inquire about results.

Emerging Research Targets

There is a growing consensus among leaders in the field of PTSD research that there are many pharmacologic agents that should be tested as novel pharmacotherapies for PTSD. The top 10 recommendations for mechanisms are presented in Table 6. To generate the preliminary data in this table, we sent surveys to 45 PTSD investigators around the world, chosen on basis of their involvement in previous VA, DoD, NIMH, and industry-sponsored PTSD clinical trials, and the PTSD Psychopharmacology Working Group, asking them to rank the top five potential new therapeutic targets for PTSD. The data were analyzed in a weighted fashion (eight points for top rank, five points for second, four points for third, three points for fourth, two points for fifth). Sixty percent ($n = 27$) of the invitees completed the survey. The top agents included rapid acting antidepressant mechanisms (ketamine-like drugs, scopolamine), cannabinoid drugs that might have anxiolytic effects or enhance extinction (cannabinoid receptor type 1 agonists, cannabidiol, fatty acid amide hydrolase inhibitors), glucocorticoid signaling, non-SRI antidepressants/monamine transporter

Table 3. Phase III Industry-Sponsored Drug Clinical Trials for the Treatment of PTSD in the United States Since 2006

Study Name	Intervention	Status	Industry Sponsor	Results
Brexpiprazole as an Additional Treatment to Paroxetine or Sertraline in Adult Patients Suffering From PTSD	Brexpiprazole vs. placebo	Terminated early	Otsuka Pharmaceuticals	Terminated due to challenges with patient eligibility

PTSD, posttraumatic stress disorder.

Table 4. Phase II Investigator-Initiated Drug Clinical Trials for PTSD in the United States Since 2006

Study Name	Intervention	Status	Funding Agency	Results
Pharmacogenetic Clinical Trial of Nepicastat for PTSD	SYN117 (nepicastat) vs. placebo	Completed (11/2009)	Department of Defense	Negative[a]
Risperidone Treatment for Military Service Related Chronic PTSD (CSP 504)	Risperidone vs. placebo	Completed (1/2011)	VA Office of Research & Development, Janssen provided drug	Negative (36)
Iloperidone for Symptoms of Arousal in PTSD	Iloperidone vs. placebo	Completed (2/2014)	University of Colorado, Novartis Pharmaceuticals (collaborator)	No published results
Ganaxolone in Posttraumatic Stress Disorder	Ganaxolone vs. placebo	Completed (3/2014)	Department of Defense, Marinus provided drug	Pending-results not published yet
Nepicastat for PTSD in OIF/OEF Veterans	Nepicastat vs. placebo	Completed (6/2014)	Department of Defense	Negative[a]
Evaluation of GSK561679 in Women With PTSD	GSK561679 vs. placebo	Completed (8/2014)	VA Office of Research & Development, National Institute of Mental Health	Negative
Glial Regulators for Testing Comorbid PTSD and Substance Use Disorders	*N*-acetylcysteine vs. placebo CPT	Completed (9/2014)	Medical University of South Carolina, Department of Defense, Institute for Translational Neuroscience	Participants treated with *N*-acetylcysteine compared with placebo evidenced significant improvements in PTSD symptoms (65).
Trial of Mifepristone in Combat Veterans With PTSD	Mifepristone vs. placebo	Recruiting	James J Peters VA Medical Center (Bronx, NY)	Ongoing
A Randomized Clinical Trial of Mifepristone in PTSD	Mifepristone vs. placebo	Recruiting	Bronx VA Medical Center, San Diego VA Medical Center, Durham VA Medical Center	Ongoing
Novel Therapeutics in PTSD: A Randomized Clinical Trial of Mifepristone	Mifepristone vs. placebo	Recruiting	VA Office of Research & Development	Ongoing
Repeated-Dose Intravenous Ketamine for PTSD	Ketamine vs. midazolam (active comparator)	Recruiting	Icahn School of Medicine at Mt. Sinai	Ongoing
CAP-Ketamine for Antidepressant Resistant PTSD	Ketamine vs. placebo	Recruiting	VA Office of Research & Development	Ongoing
Zonisamide in Addition to E-CPT-C for Veterans With PTSD and Comorbid Alcohol Dependence	Zonisamide vs. placebo E-CPT-C	Recruiting	Department of Defense	Ongoing

CPT, Cognitive Processing Therapy; E-CPT-C, Enhanced Cognitive Processing Therapy-C; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; PTSD, posttraumatic stress disorder; VA, Veterans Affairs.

[a]L. Davis, M.D., personal communication, Feb 17, 2017.

antagonists (trazodone, vortioxetine, cyclobenzaprine, etc.), opioids (buprenorphine, kappa opioid receptor antagonists), riluzole, and other mechanisms. There are already completed or ongoing trials with several of these agents, including ketamine, glucocorticoids, and riluzole. Pharmacologic agents exist that could be studied for the remainder of these mechanisms. Further, the survey identified many other promising mechanisms that were not currently being studied in humans. Last, it should be acknowledged that our understanding of the pathophysiology of PTSD is limited. Thus, we expect the list of priority therapeutic targets to evolve with advances in our understanding of the neurobiology of PTSD (Table 7).

Table 5. Phase III Investigator-Initiated Drug Clinical Trials for PTSD in the United States Since 2006

Study Name	Intervention	Status	Funding Agency	Results
Levetiracetam in PTSD	Levetiracetam vs. placebo	Completed (3/2008)	Duke University, UCB Pharma	No published results
CSP 563: Prazosin and Combat Trauma PTSD	Prazosin vs. placebo	Completed (5/2013)	VA Office of Research & Development	Negative[a]
Prazosin for Treatment of Patients With Alcohol Dependence and PTSD	Prazosin vs. placebo	Completed (10/2014)	Department of Defense and VA VISN 1	Negative (59)
Prazosin for Nightmares and Sleep Disturbance	Prazosin vs. placebo	Completed (2/16/2006)	VA Office of Research and Development and NIMH	Positive (40)
Prazosin for Combat Trauma PTSD	Prazosin vs. placebo	Completed (8/29/2012)	VA Office of Research (VISN 20 MIRECC)	Positive (41)

CSP, Cooperative Studies Program; MIRECC, Mental Illness Research, Education and Clinical Centers; NIMH, National Institute of Mental Health; PTSD, posttraumatic stress disorder; VA, Veterans Affairs; VISN, Veterans Integrated Service Network.

[a]M. Raskind, M.D., personal communication, Feb 1, 2017.

Table 6. Top Therapeutic Targets for PTSD From Expert Group ($N = 27$)

Target	Score
NMDA Receptor Antagonists	78
Cannabinoid Receptor Modulators	70
Glucocorticoid Receptor Agonists	58
Non-SRI Antidepressants	50
Opioid Receptor Agonists	25
Alpha-1 Adrenergic Receptor Antagonists	21
$5HT_2$-D_2 Receptor Antagonist (Other Than Risperidone)	20
Riluzole	18
Alpha-2 Adrenergic Receptor Agonists	18
NPY Receptor Modulators	10
Glucocorticoid Low-Activity Partial Agonists And/Or Antagonist	10
Orexin Receptor Antagonists	9
NMDA Receptor Coagonists	9
Anticonvulsants	8
D_2 Receptor Agonists	8

D_2, dopamine type 2; NMDA, *N*-methyl-D-aspartate; NPY, neuropeptide Y; PTSD, posttraumatic stress disorder; SRI, serotonin reuptake inhibitor; $5\text{-}HT_2$, 5-hydroxytryptamine-2.

Conclusions of the VA PTSD Psychopharmacology Work Group: Growing the Portfolio of PTSD Pharmacotherapy Research

1. The urgent need to find effective pharmacologic treatments for PTSD should be considered a national mental health priority. There is a serious knowledge gap related to the efficacy of commonly prescribed medications and novel compounds for the treatment of PTSD that impedes the effective treatment of PTSD. There is a need for clinical trials conducted in veterans that support the efficacy of pharmacologic treatment of PTSD within the VA. Further, there is a need for this research to include adequate numbers of female veterans so that research findings will be relevant to this important group of veterans. In other populations, the same holds for most pharmacologic treatments other than SRIs. The current number of investigator-initiated and pharmaceutical industry–initiated clinical trials is inadequate to meet the needs for more effective PTSD pharmacotherapy. Several factors may contribute to this deficit: 1) inadequate psychopharmacology research workforce, 2) a need for novel opportunities and supporting funding mechanisms to "prime the pump" for PTSD pharmacotherapy research including mission-driven funding mechanisms, and 3) strengthening of collaborations among the pharmaceutical industry, government, and academia to reduce risk for pharmaceutical companies entering PTSD research and to accelerate the transition from novel insights into the neurobiology of PTSD to clinical trials.
2. There is a need to increase the number of early-phase clinical trials through novel collaborations between government, industry, and academia. Advances in the study of the neurobiology of stress effects in animal models and PTSD implicate a growing number potential targets for the treatment of PTSD. It is important to explore more novel treatments for PTSD based on a biological rationale to identify what new compounds hold promise. Informal discussions with representatives of the pharmaceutical industry suggest that PTSD is a frequent clinical target considered in the drug development process. There is a need for an ongoing effort for the VA and other funding organizations to engage these companies on a proactive basis to encourage medication development for PTSD and to develop efficient mechanisms for partnering (financial support, infrastructure support) with these companies while enabling them to retain the intellectual property as an incentive for developing positive findings into new FDA indications. VA Research and Development has taken recommendations from the expert Working Group to develop a new effort, the PTSD Psychopharmacology Initiative, that will continue to respond to recommendations to focus more systematically on finding medications for effectively treating PTSD.
3. There is a need to develop new trial designs and/or methodologies specifically in the area of PTSD psychopharmacology trials for the following purposes: 1) the identification of novel treatments targeting specific symptoms that might be represented by distinct circuits, 2) informing the optimal combination of medication and psychosocial treatments, and 3) characterizing the real-world effectiveness of the numerous medications already frequently prescribed for the treatment of PTSD.
4. Foundational studies are required to inform the optimal prescription of commonly prescribed medications for the treatment of PTSD. The risks and the costs of ineffective treatments, combined with the opportunity for improving the treatment of PTSD, necessitates the conduct of studies that would serve to provide critical basic information about the optimal treatment of PTSD. It would answer basic

Table 7. Recommendations

• The urgent need to find effective pharmacologic treatments for PTSD should be considered a national mental health priority.
• There is a need to increase the number of early phase clinical trials through novel collaborations among government, industry, and academia.
• There is a need to develop new trial designs and/or methodologies specifically in the area of PTSD psychopharmacology trials.
• Foundational studies are required to inform the optimal prescription of commonly prescribed medications for the treatment of PTSD.
• The development of a psychopharmacology clinical trials workforce and infrastructure for PTSD would advance the goal of increasing clinical trials in this area.
• Studies exploring the pathophysiology of PTSD will be critical to inform the rational development of novel pharmacologic interventions.
• There is a need to continue to invest in initiatives in translational neuroscience to enhance the expansion of the pipeline of new PTSD pharmacotherapeutics.

PTSD, posttraumatic stress disorder.

questions including the following: 1) What is the rate of antidepressant-resistant symptoms of PTSD? 2) Is it better to add particular adjunctive medications or switch antidepressants? and 3) Are there commonly prescribed medications that are ineffective or present risks that outweigh benefits and should be avoided? With NIMH support, this type of foundational study has been conducted in depression, schizophrenia, autism, and Alzheimer's disease. The STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study may be particularly informative in its design (60–62), as many of the medications and treatment strategies for PTSD derive from those developed for depression. Although there is tremendous need for sequential, multiple assignment, randomized trial in PTSD, there are questions whether the commonly prescribed medications are adequately validated to support a study of this kind. It is possible that preparatory studies might be needed to determine preliminary efficacy and optimal dosing.

5. The development of a psychopharmacology clinical trials workforce and infrastructure for PTSD would advance the goal of increasing clinical trials in this area. Steps that might be taken to advance this objective include training clinician scientists as well as biostatisticians and trialists including supporting career development awards focused on this topic, and developing opportunities for this group of investigators to participate in clinical trials funded through new funding mechanisms.
6. Studies exploring the pathophysiology of PTSD will be critical to inform the rational development of novel pharmacologic interventions. Our knowledge of the complex neurobiology of PTSD is limited. This limits our ability to rationally select new drug targets. Pathophysiological research must proceed in parallel with clinical trials studies to information the selection of the next generation of novel therapeutics for PTSD.
7. There is a need to continue to invest in initiatives in translational neuroscience to enhance the expansion of the pipeline of new PTSD pharmacotherapeutics. To support hypothesis-based testing of novel therapeutics for PTSD, there is a need to invest in translational neuroscience studies of fear and stress, the pathophysiology of PTSD, and proof-of-mechanism and proof-of-principle studies of novel therapeutics.

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