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 three-fold. 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 Working 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
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 (SSRI) 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, predominate 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 psychophysioic characteristics. For example, risperidone may be helpful for
ptd of psychopathology project grants by federal funding agencies, there was a commensurate increase in the number of independent PTSD pharmacology studies. a search of national institutes of health eporter on December 5, 2016, for va and nih PTSD medication trials and related initiatives. a biological psychiatry psychopharmacology project grants by federal funding agencies, there was a commensurate increase in the number of independent PTSD pharmacology studies.

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 caution in extrapolating data from 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.

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

<table>
<thead>
<tr>
<th>Category</th>
<th>2004</th>
<th>2007</th>
<th>2010</th>
<th>2013</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New PTSD Episodes</strong></td>
<td>51,750</td>
<td>69,604</td>
<td>84,850</td>
<td>82,546</td>
<td>731,520</td>
</tr>
<tr>
<td><strong>Mean Number of Psychotropics</strong></td>
<td>3.5 ± 2.5</td>
<td>3.5 ± 2.6</td>
<td>3.6 ± 2.7</td>
<td>3.5 ± 2.7</td>
<td>3.5 ± 2.7</td>
</tr>
<tr>
<td><strong>All Antidepressants</strong></td>
<td>85.1 (44,026)</td>
<td>82.7 (57,544)</td>
<td>80.1 (68,001)</td>
<td>78.0 (64,394)</td>
<td>81.0 (592,505)</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>5.7 (2948)</td>
<td>4.6 (3195)</td>
<td>3.8 (3221)</td>
<td>3.7 (3074)</td>
<td>4.2 (31,019)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>12.4 (6592)</td>
<td>12.3 (8579)</td>
<td>12.9 (10,973)</td>
<td>13.0 (10,722)</td>
<td>12.6 (92,460)</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>1.2 (638)</td>
<td>0.3 (237)</td>
<td>0.1 (116)</td>
<td>0.1 (50)</td>
<td>0.3 (2097)</td>
</tr>
<tr>
<td>Phenerazine</td>
<td>0.0 (20)</td>
<td>0.0 (10)</td>
<td>0.0 (8)</td>
<td>0.0 (8)</td>
<td>0.0 (92)</td>
</tr>
<tr>
<td>Trazodone</td>
<td>33.4 (17,296)</td>
<td>32.3 (22,484)</td>
<td>30.5 (25,847)</td>
<td>29.7 (24,489)</td>
<td>31.0 (226,812)</td>
</tr>
<tr>
<td>Any SSRI or SNRI</td>
<td>70.1 (36,290)</td>
<td>67.6 (47,064)</td>
<td>65.7 (55,740)</td>
<td>63.1 (52,112)</td>
<td>66.3 (485,194)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>13.9 (7212)</td>
<td>11.8 (6246)</td>
<td>9.5 (8022)</td>
<td>11.5 (9481)</td>
<td>11.3 (82,346)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10.3 (5331)</td>
<td>7.0 (4842)</td>
<td>5.0 (4266)</td>
<td>6.0 (4951)</td>
<td>6.6 (48,215)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>26.0 (13,449)</td>
<td>16.3 (11,367)</td>
<td>21.4 (18,145)</td>
<td>31.2 (25,771)</td>
<td>22.9 (167,613)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>9.2 (4770)</td>
<td>8.5 (5882)</td>
<td>8.4 (7121)</td>
<td>11.7 (9680)</td>
<td>9.1 (66,747)</td>
</tr>
<tr>
<td>All Anticonvulsants</td>
<td>21.8 (11,267)</td>
<td>22.8 (15,871)</td>
<td>26.0 (22,080)</td>
<td>29.1 (24,005)</td>
<td>24.9 (182,077)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>11.1 (5739)</td>
<td>12.1 (8399)</td>
<td>15.2 (12,851)</td>
<td>18.2 (15,001)</td>
<td>14.1 (102,791)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>2.1 (1072)</td>
<td>2.6 (1832)</td>
<td>3.3 (2764)</td>
<td>4.3 (3517)</td>
<td>3.1 (220,307)</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>7.3 (3794)</td>
<td>6.8 (4723)</td>
<td>6.8 (5732)</td>
<td>6.2 (5152)</td>
<td>6.7 (49,197)</td>
</tr>
<tr>
<td>Prazosin</td>
<td>6.1 (3171)</td>
<td>9.6 (6690)</td>
<td>17.3 (14,641)</td>
<td>25.8 (21,291)</td>
<td>15.0 (101,048)</td>
</tr>
<tr>
<td>All Atypical Antipsychotics</td>
<td>29.7 (15,390)</td>
<td>23.8 (16,562)</td>
<td>20.3 (17,185)</td>
<td>18.9 (13,944)</td>
<td>21.8 (159,757)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>4.5 (2347)</td>
<td>1.9 (1342)</td>
<td>1.7 (1444)</td>
<td>1.6 (1298)</td>
<td>2.0 (14,691)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>18.9 (9758)</td>
<td>15.8 (10,970)</td>
<td>11.5 (9728)</td>
<td>9.0 (7426)</td>
<td>13.3 (97,542)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>9.9 (5126)</td>
<td>6.1 (4248)</td>
<td>5.1 (4323)</td>
<td>4.7 (3917)</td>
<td>5.8 (42,311)</td>
</tr>
<tr>
<td>All Typical Antipsychotics</td>
<td>1.8 (946)</td>
<td>1.8 (1275)</td>
<td>1.8 (1526)</td>
<td>1.8 (1485)</td>
<td>1.8 (13,304)</td>
</tr>
<tr>
<td>All Addiction Medicines*</td>
<td>7.8 (4027)</td>
<td>12.4 (8665)</td>
<td>12.9 (10,984)</td>
<td>12.9 (10,637)</td>
<td>11.9 (87,361)</td>
</tr>
<tr>
<td>All Sedative Hypnotics</td>
<td>38.2 (19,776)</td>
<td>37.9 (26,353)</td>
<td>41.3 (35,085)</td>
<td>35.4 (29,262)</td>
<td>38.9 (284,877)</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>4.6 (2404)</td>
<td>7.9 (5532)</td>
<td>18.2 (15,472)</td>
<td>14.3 (11,837)</td>
<td>13.0 (85,086)</td>
</tr>
<tr>
<td>Any benzodiazepine</td>
<td>34.9 (18,066)</td>
<td>32.9 (22,907)</td>
<td>29.4 (24,979)</td>
<td>25.1 (20,756)</td>
<td>30.3 (221,309)</td>
</tr>
<tr>
<td>All Opioids*</td>
<td>35.4 (18,325)</td>
<td>37.8 (26,301)</td>
<td>38.3 (32,473)</td>
<td>34.6 (28,564)</td>
<td>36.9 (270,103)</td>
</tr>
<tr>
<td>All Stimulants</td>
<td>1.1 (592)</td>
<td>1.5 (1060)</td>
<td>2.3 (1991)</td>
<td>3.3 (2702)</td>
<td>2.1 (15,690)</td>
</tr>
<tr>
<td>Lithium</td>
<td>1.8 (942)</td>
<td>1.4 (951)</td>
<td>1.4 (1162)</td>
<td>1.5 (1254)</td>
<td>1.4 (10,580)</td>
</tr>
<tr>
<td>Buspirone</td>
<td>5.1 (2665)</td>
<td>4.7 (3241)</td>
<td>4.9 (4168)</td>
<td>6.4 (5269)</td>
<td>5.1 (37,614)</td>
</tr>
</tbody>
</table>

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 inhibitor; SSRI, selective serotonin reuptake inhibitors.

*Includes acamprosate, buprenorphine, disulfiram, naltrexone, nicotine replacement, and varenicline.

**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 United States, conducted by academic investigators in
have been 13 investigator-initiated Phase II clinical trials in
the treatment of PTSD in the United States. The drugs and
affected individuals and society in general. Over the past 10
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 pharmace-
autical 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), cannabinoic drugs that might have axio-
lytic effects or enhance extinction (cannabinoid receptor type 1
agonists, cannabidiol, fatty acid amide hydrolase inhibitors),
glucoecorticoid signaling, non-SRI antidepressants/monamine
transporter antagonists (trazodone, vortioxetine, cyclobenzap-

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

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Intervention</th>
<th>Status</th>
<th>Industry Sponsor</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brexpiprazole vs. placebo</td>
<td>Completed</td>
<td>GlaxoSmithKline</td>
<td>Early study termination and small sample size precluded making any definitive efficacy conclusions (63).</td>
<td></td>
</tr>
<tr>
<td>7-Keto DHEA for the Treatment of PTSD</td>
<td>Completed</td>
<td>Humanetics Corporation</td>
<td>No published results</td>
<td></td>
</tr>
<tr>
<td>Safety &amp; Efficacy Study of TNX-102 SL in Subjects With Military-Related PTSD &amp; Related Conditions</td>
<td>Completed</td>
<td>Tonix Pharmaceuticals</td>
<td>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).</td>
<td></td>
</tr>
<tr>
<td>Open Label Extension Safety &amp; Efficacy Study of TNX-102 SL Tablets in Military Related PTSD &amp; Related Conditions</td>
<td>Completed</td>
<td>Tonix Pharmaceuticals</td>
<td>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).</td>
<td></td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Intervention</th>
<th>Status</th>
<th>Industry Sponsor</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brexpiprazole as an Additional Treatment to Paroxetine or Sertraline in Adult Patients Suffering From PTSD</td>
<td>Terminated early</td>
<td>Otsuka Pharmaceuticals</td>
<td>Terminated due to challenges with patient eligibility</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Intervention</th>
<th>Status</th>
<th>Funding Agency</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacogenetic Clinical Trial of Nepicastat for PTSD</td>
<td>SYN117 (nepicastat) vs. placebo</td>
<td>Completed (11/2009)</td>
<td>Department of Defense</td>
<td>Negative</td>
</tr>
<tr>
<td>Risperidone Treatment for Military Service Related Chronic PTSD (CSP 504)</td>
<td>Risperidone vs. placebo</td>
<td>Completed (1/2011)</td>
<td>VA Office of Research &amp; Development, Janssen provided drug</td>
<td>Negative (36)</td>
</tr>
<tr>
<td>Iloperidone for Symptoms of Arousal in PTSD</td>
<td>Iloperidone vs. placebo</td>
<td>Completed (2/2014)</td>
<td>University of Colorado, Novartis Pharmaceuticals (collaborator)</td>
<td>No published results</td>
</tr>
<tr>
<td>Ganaxalone in Posttraumatic Stress Disorder</td>
<td>Ganaxalone vs. placebo</td>
<td>Completed (3/2014)</td>
<td>Department of Defense, Marinus provided drug</td>
<td>Pending-results not published yet</td>
</tr>
<tr>
<td>Nepicastat for PTSD in OIF/OEF Veterans</td>
<td>Nepicastat vs. placebo</td>
<td>Completed (6/2014)</td>
<td>Department of Defense</td>
<td>Negative</td>
</tr>
<tr>
<td>Evaluation of GSK561679 in Women With PTSD</td>
<td>GSK561679 vs. placebo</td>
<td>Completed (8/2014)</td>
<td>VA Office of Research &amp; Development, National Institute of Mental Health</td>
<td>Negative</td>
</tr>
<tr>
<td>Glial Regulators for Testing Comorbid PTSD and Substance Use Disorders</td>
<td>N-acetylcysteine vs. placebo CPT</td>
<td>Completed (9/2014)</td>
<td>Medical University of South Carolina, Department of Defense, Institute for Translational Neuroscience</td>
<td>Participants treated with N-acetylcysteine compared with placebo evidenced significant improvements in PTSD symptoms (63).</td>
</tr>
<tr>
<td>Trial of Mifepristone in Combat Veterans With PTSD</td>
<td>Mifepristone vs. placebo</td>
<td>Recruiting</td>
<td>James J Peters VA Medical Center (Bronx, NY)</td>
<td>Ongoing</td>
</tr>
<tr>
<td>A Randomized Clinical Trial of Mifepristone in PTSD</td>
<td>Mifepristone vs. placebo</td>
<td>Recruiting</td>
<td>Bronx VA Medical Center, San Diego VA Medical Center, Durham VA Medical Center</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Novel Therapeutics in PTSD: A Randomized Clinical Trial of Mifepristone</td>
<td>Mifepristone vs. placebo</td>
<td>Recruiting</td>
<td>VA Office of Research &amp; Development</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Repeated-Dose Intravenous Ketamine for PTSD</td>
<td>Ketamine vs. midazolam (active comparator)</td>
<td>Recruiting</td>
<td>Icahn School of Medicine at Mt. Sinai</td>
<td>Ongoing</td>
</tr>
<tr>
<td>CAP-Ketamine for Antidepressant Resistant PTSD</td>
<td>Ketamine vs. placebo</td>
<td>Recruiting</td>
<td>VA Office of Research &amp; Development</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Zonisamide in Addition to E-CPT-C for Veterans With PTSD and Comorbid Alcohol Dependence</td>
<td>Zonisamide vs. placebo</td>
<td>Recruiting</td>
<td>Department of Defense</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

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.

*L. Davis, M.D., personal communication, Feb 17, 2017.

ine, 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 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

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

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.

*M. Raskind, M.D., personal communication, Feb 1, 2017.
Table 6. Top Therapeutic Targets for PTSD From Expert Group (N = 27)

<table>
<thead>
<tr>
<th>Target</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDA Receptor Antagonists</td>
<td>78</td>
</tr>
<tr>
<td>Cannabinoid Receptor Modulators</td>
<td>70</td>
</tr>
<tr>
<td>Glucocorticoid Receptor Agonists</td>
<td>58</td>
</tr>
<tr>
<td>Non-SRI Antidepressants</td>
<td>50</td>
</tr>
<tr>
<td>Opioid Receptor Agonists</td>
<td>25</td>
</tr>
<tr>
<td>Alpha-1 Adrenergic Receptor Antagonants</td>
<td>21</td>
</tr>
<tr>
<td>SHT₂-D₂ Receptor Antagonist (Other Than Risperidone)</td>
<td>20</td>
</tr>
<tr>
<td>Riluzole</td>
<td>18</td>
</tr>
<tr>
<td>Alpha-2 Adrenergic Receptor Agonants</td>
<td>18</td>
</tr>
<tr>
<td>NPY Receptor Modulators</td>
<td>10</td>
</tr>
<tr>
<td>Glucocorticoid Low-Activity Partial Agonists And/Or Antagonist</td>
<td>10</td>
</tr>
<tr>
<td>Orexin Receptor Antagonants</td>
<td>9</td>
</tr>
<tr>
<td>NMDA Receptor Coagonists</td>
<td>9</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>8</td>
</tr>
<tr>
<td>D₂ Receptor Agonists</td>
<td>8</td>
</tr>
</tbody>
</table>

D₂, dopamine type 2; NMDA, N-methyl-D-aspartate; NPY, neuropeptide Y; PTSD, posttraumatic stress disorder; SRI, serotonin reuptake inhibitor; 5-HT₂, 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.

JHK has received grant/research support from the National Institutes of Health, Pfizer, AstraZeneca, and National Institute on Alcohol Abuse and Alcoholism; has served as scientific consultant for AMGEN, AstraZeneca, Biogen, Idec, MA, Biomedisyn Corporation, Forum Pharmaceuticals, Janssen Research & Development, Otsuka America Pharmaceuticals, Sunovion Pharmaceuticals, Takeda Industries, and Taisho Pharmaceuticals; has served on the scientific advisory board for Biohaven Pharmaceuticals, Blackthorn Therapeutics, Lohocia Research Corporation, Luc Therapeutics, Pfizer Pharmaceuticals, and TRIMaran Pharma; owns stock and/or stock options in ArRETT Neuroscience, Biohaven Pharmaceuticals Medical Services, Blackhorn Therapeutics, and Luc Therapeutics; serves as Editor for Biological Psychiatry; and holds patents for Dopamine and Noradrenergic Reuptake Inhibitors in Treatment of Schizophrenia, U.S. Patent No. 5,447,948 (issued Sep 5, 1995); Glutamate Modulating Agents in the Treatment of Mental Disorders, U.S. Patent No. 8,778,979 (issued Jul 15, 2014); Intranasal Administration of Ketamine to Treat Depression, U.S. Application No. 14/197,767 (filed Mar 5, 2014), United States application or PCT International application No. 14/306,382 (filed June 17, 2014); Methods for Treating Suicidal Ideation, U.S. Application No. 14/197,767 (filed March 5, 2014); Composition and Methods to Treat Addiction, Provisional US Patent Application No. 61/973,961 (April 2, 2014); Treatment Selection for Major Depressive Disorder, USPTO docket number Y0087.70116US00 (filed June 3, 2016); Compounds, Compositions and Methods for Treating or Preventing Depression and Other Diseases, U.S. Provisional Patent Application No. 62,408,983 (filed October 17, 2016). LLD has received research funding to an institutional affiliate from Tonix, Merck, and Allergan and personal compensation as a consultant from Otsuka. TCN has received study medication from Actelion and GlaxoSmithKline and has served on an scientific advisory board for Resilience Therapeutics and Insys Therapeutics. TCN has received grant support from the National Institute of Mental Health, Department of Veterans Affairs, and Department of Defense. MR has served as a consultant to Takeda Pharmaceuticals and to Merck Pharmaceuticals. He received research grant funding from Lilly Pharmaceuticals, the National Institutes of Health, the Department of Veterans Affairs, and the Department of Defense. PPS received grant support from the Department of Veterans Affairs and Department of Defense. MBS has been a consultant to Actelion, Dart Neuroscience, Healthcare Management Technologies, Neurocrine, Oxeia Biopharmaceuticals, Janssen, Pfizer, and Resilience Therapeutics. He also reported stock options with Oxeia Biopharmaceuticals and Resilience Therapeutics. He is also paid for editorial work on Biological Psychiatry and Up-To-Date. BS is supported by a VA Health Services Research and Development Career Development Award. All other authors report no biomedical financial interests or potential conflicts of interest.

Article Information

From the Departments of Psychiatry and Neurosciences (JHK), Yale University School of Medicine, New Haven; Clinical Neuroscience Division (JHK, JV), National Center for PTSD; Psychiatry Services (JHK, JV), VA Connecticut Healthcare System, West Haven, Connecticut; Research and Development Service (LLD), Tuscaloosa VA Medical Center, Tuscaloosa; Department of Psychiatry (LLD), University of Alabama School of Medicine, Birmingham, Alabama; Department of Psychiatry (TCN), University of California, San Francisco; San Francisco VA Medical Center (TCN), San Francisco; Departments of Psychiatry and Family Medicine & Public Health (MBS), University of California, San Diego, La Jolla; VA San Diego Healthcare System (MBS), San Diego, California; Department of Psychiatry and Behavioral Sciences (MR), University of Washington School of Medicine; VA Puget Sound Health Care System (MR), Seattle, Washington; Executive Division (PPS, BS), National Center for PTSD; Department of Psychiatry (PPS, BS), Geisel School of Medicine at Dartmouth, White River Junction, Vermont; VA Office of Research and Development (TG), and VA Cooperative Studies Program Central Office (GDRh), VA Office of Research and Development, Washington, DC.

Address correspondence to John H. Krystal, M.D., Yale University School of Medicine, 300 George St #901, New Haven, CT 06510; E-mail: john.krystal@yale.edu.

Received Jan 20, 2017; revised Mar 2, 2017; accepted Mar 7, 2017.

Acknowledgments and Disclosures

This work was supported by the VA Office of Research and Development Clinical Science Research & Development Service and Cooperative Studies Program. The views expressed in this article are those of the authors and do not represent the views of the U.S. Department of Veterans Affairs or the U.S. Government.
References


Correspondence


