Continuing Medical Education Commercial Disclosure

The presenter, Terri Gleason, Ph.D., Director of Clinical Science Research & Development Service, Department of Veterans Affairs. has no (zero) commercial relationships to disclose

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VA Office of Research & Development
Psychopharmacology Research

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American Society for Clinical Psychopharmacology
May 2019

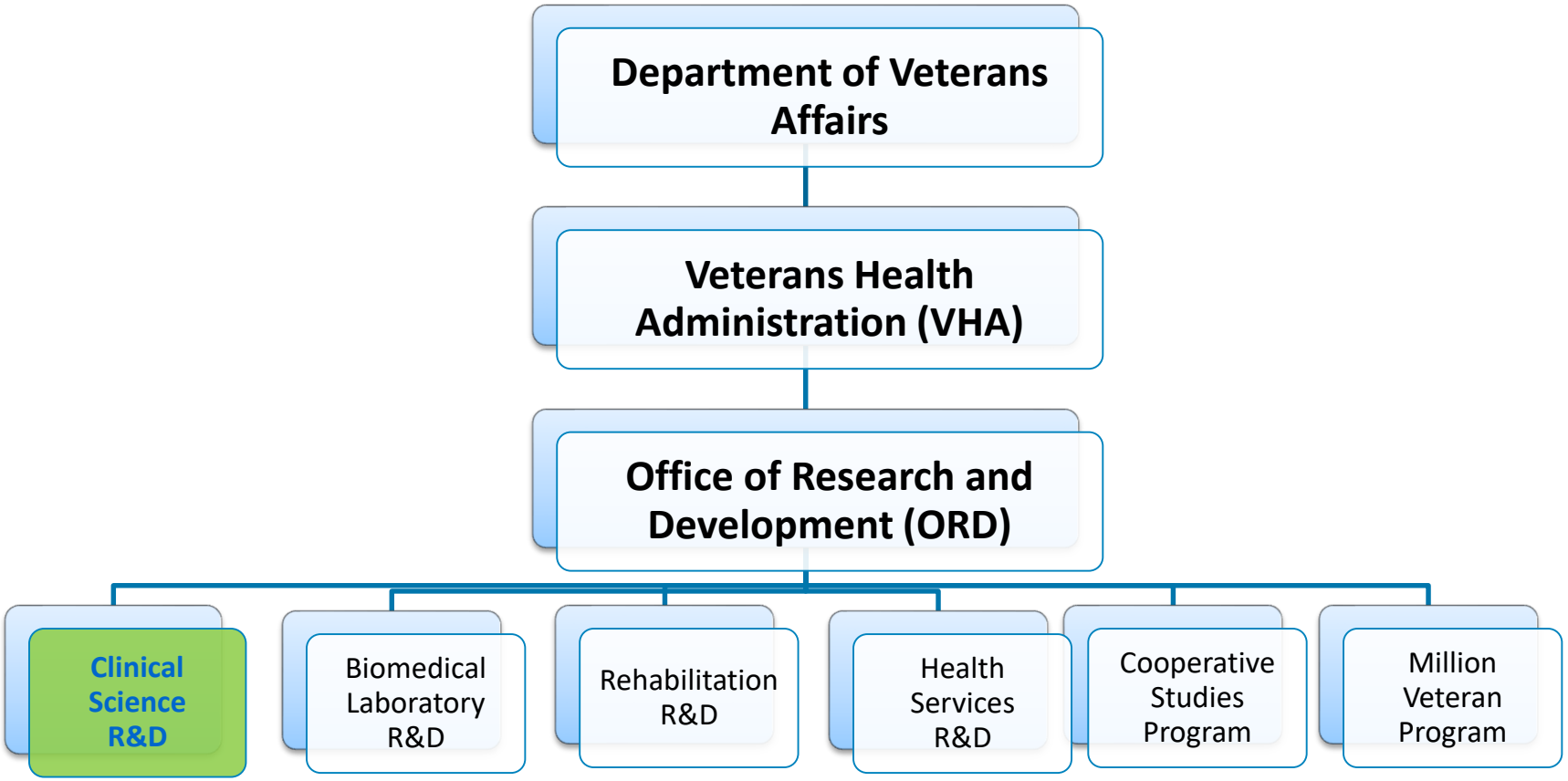
VA | U.S. Department of Veterans Affairs
Veterans Health Administration
Office of Research & Development

Objectives

- VA Research – Overview
- PTSD Psychopharmacology Initiative
- How to Collaborate with VA
- Dissemination/Implementation of Research Results

VA Office of Research & Development (ORD) Overview

Organizational Structure



VA Office of Research & Development
MISSION

- To improve Veterans' health and well-being via basic, translational, clinical, rehabilitative and health services research

- To attract, train, and retain the highest-caliber investigators, and nurture their development as leaders in their fields

- To assure a culture of professionalism, collaboration, accountability, and the highest regard for research volunteers' safety and privacy

ORD Snapshot

- ORD currently funds approximately 2,700 intramural research projects, including individual investigator awards, large clinical trials, research centers, and career development awards
- Approximately 20% of applicants are successful in any given funding round
- Approximately 50% of VA investigators are clinicians
- ORD depends on close ties to academic affiliates
- ORD partners extensively – public and private entities

PTSD Research in VA

PTSD Research in VA

- PTSD is a research priority for VA Research with much activity centered on supporting studies to advance treatment for this condition
- VA ORD (across all services) currently funds over 180 projects on PTSD
- During FY18, PTSD funding included studies across the research spectrum in every ORD research service, with Million Veteran Program (MVP), in support of medication trials, and co-funding a PTSD clinical trials consortium with DoD (Consortium to Alleviate PTSD)
- Important collaborations with other federal agencies, stakeholders and industry

Selected Major Accomplishments in VA PTSD Research

- **1989:** Created the National Center for PTSD to address the needs of Veterans and other trauma survivors with PTSD
- **2007:** Confirmed the value of prolonged exposure therapy as a treatment for women Veterans with PTSD
- **2013:** Funded, along with the Department of Defense, two consortia to improve treatment for PTSD and mild traumatic brain injury (mTBI)
- **2014:**
  - Found that cognitive processing therapy delivered via videoconferencing is as effective for PTSD as in-person therapy
  - Found that Veterans who sought and received care soon after the end of their service had lower rates of PTSD than those who waited to get treatment
  - Established the VA National PTSD Brain Bank
- **2016:**
  - Announced the PTSD Psychopharmacology Initiative to foster work on identifying, testing, and confirming the most effective PTSD medications for Veterans
  - Learned that Veterans with PTSD had different patterns of brain activity than Veterans with mTBIs
- **2017:** Found that prolonged exposure therapy could be delivered as effectively by videoconferencing as in person

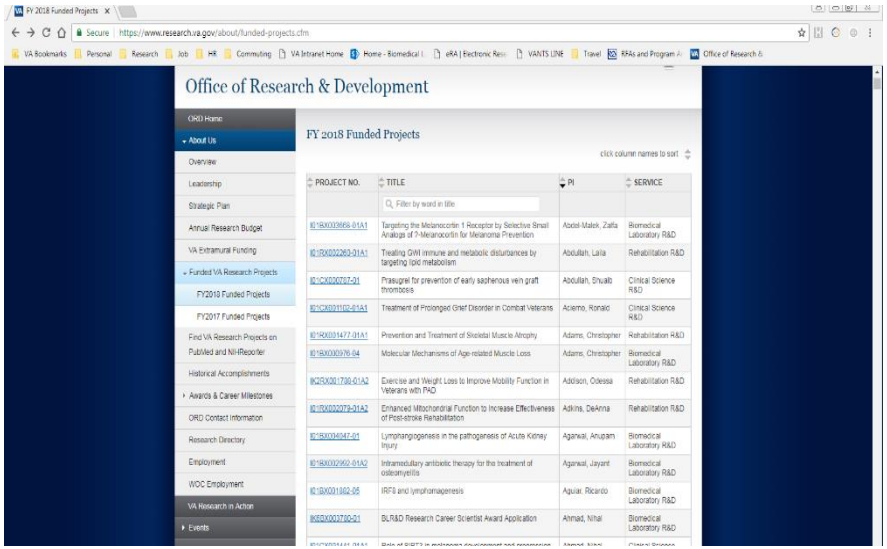
FY18 PTSD Projects

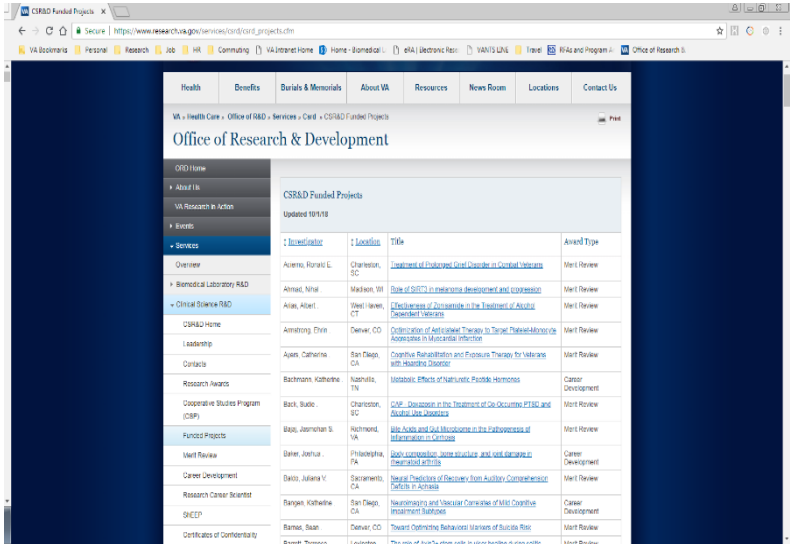
Program Award	# of Projects	FY18 Total $
Administration	1	$9,588
Career Development / Capacity Building	36	$4,890,043
Center	2	$2,573,121
Fellows	2	$5,882
Merit Review	108	$20,050,933
Multiple Site Study	9	$6,435,071
Pilot Study	13	$584,552
Presidential Early Career Award	1	$25,000
REAP	2	$627,485
Research Career Scientist Award	4	$777,293
Senior Service Award	2	$100,000
Service Directed Research Program	1	$299,274

- 57 Clinical Trials
- 6 Cooperative Study Program projects
- 6 PTSD Medication Studies

Finding ORD PTSD Studies

- Overview of VA research on PTSD- https://www.research.va.gov/topics/ptsd.cfm
- VA Research Currents-- https://www.research.va.gov/currents/default.cfm
- Funded Projects--https://www.research.va.gov/about/funded-projects.cfm





PTSD Project Highlight

Genomics of Posttraumatic Stress Disorder among Veterans

[CSP #575B] (VA: Stein & Gelernter)

Objective: Use Million Veteran Program data to identify genes associated with PTSD risk of combat-exposed patients with PTSD and combat-exposed control patients without PTSD

- One of the largest genomic studies ever done on PTSD

1. Examine MVP-obtained data and electronic health record (EHR) data to implement methods for identification
2. Assemble and validate a study population of 20,000 participants—(10,000 cases and 10,000 controls)
3. Conduct genetic analyses ("genotyping") comparing the cases to controls, to identify genes associated with increased risk of developing the condition

PTSD Project Highlight

Veterans Individual Placement and Support (IPS) Towards Advancing Recovery (VIP-STAR) [CSP #589] (VA: Davis)

- Objective: A prospective, multisite, randomized clinical trial that included 541 unemployed Veterans with PTSD at 12 Veterans Affairs medical center comparing outcomes for PTSD patients who are in the IPS employment program with those in the more traditional Transitional Work Program (daily workshop programs on site)
- Demonstrated significantly greater effectiveness of IPS-supported employment over stepwise transitional work vocational rehabilitation for veterans living with chronic PTSD. The results provide supporting evidence for increasing access to IPS for veterans living with PTSD.
- Next steps include wider spread within VA and public private partnership support

PTSD Psychopharmacology Initiative (PPI)

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

Biol. Psyc. Oct 1, 2017; 82: e51-e59

Medications For PTSD - Challenges

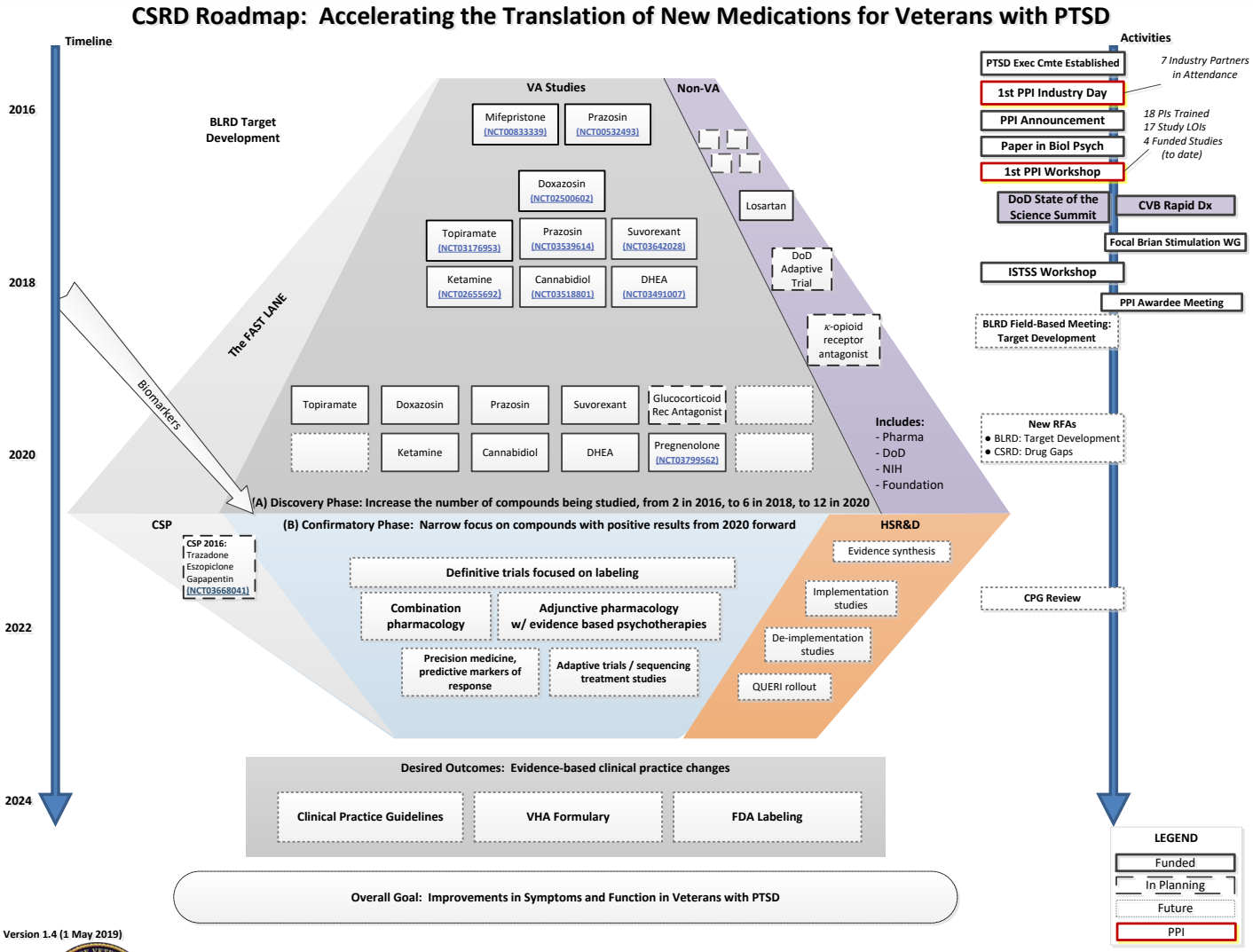
- Substantial heterogeneity in clinical presentation and biological underpinnings of PTSD
- Over past 30 years, 130+ clinical trials conducted with 48 drug or drug combinations, encompassing 30+ mechanisms of action, with little to no return on investment
- Currently only two FDA-approved drugs for the treatment of PTSD despite efforts between government agencies, academic centers, pharmaceutical companies, non-profits, etc., to develop new treatments

VA PTSD PSYCHOPHARMACOLOGY INITIATIVE (PPI)

Announced - December 2016

- Call for study proposals focused on PTSD medications with submission from qualified VA investigators
- PTSD Pharmacotherapy Clinical trial training workshop for VA investigators

PPI Roadmap



Version 1.4 (1 May 2019)

Currently Funded PTSD Medication Studies

- Doxazosin
- Suvorexant
- Ketamine
- Cannabidiol
- Neurosteroids
- Topiramate
- DHEA
- **AND - WE NEED TO IDENTIFY OTHER COMPOUNDS TO TEST, NOVEL / REPURPOSED, to completely cover possibilities for treating PTSD**

PPI ACCOMPLISHMENTS

- Formed an Executive Committee to review progress and recommend actions
- Published state of crisis/need, *Biological Psychiatry*
- Sponsored a VA Industry Day to attract pharmaceutical partners
- Training Workshop (May 2017) produced 18 trained/PPI mentored scientists
- In addition to 2 ongoing trials, 6 new PPI clinical trials and large CSP comparative effectiveness trial of commonly used sleeping medications have been approved
- Of the current funded studies, 4 have industry partnerships

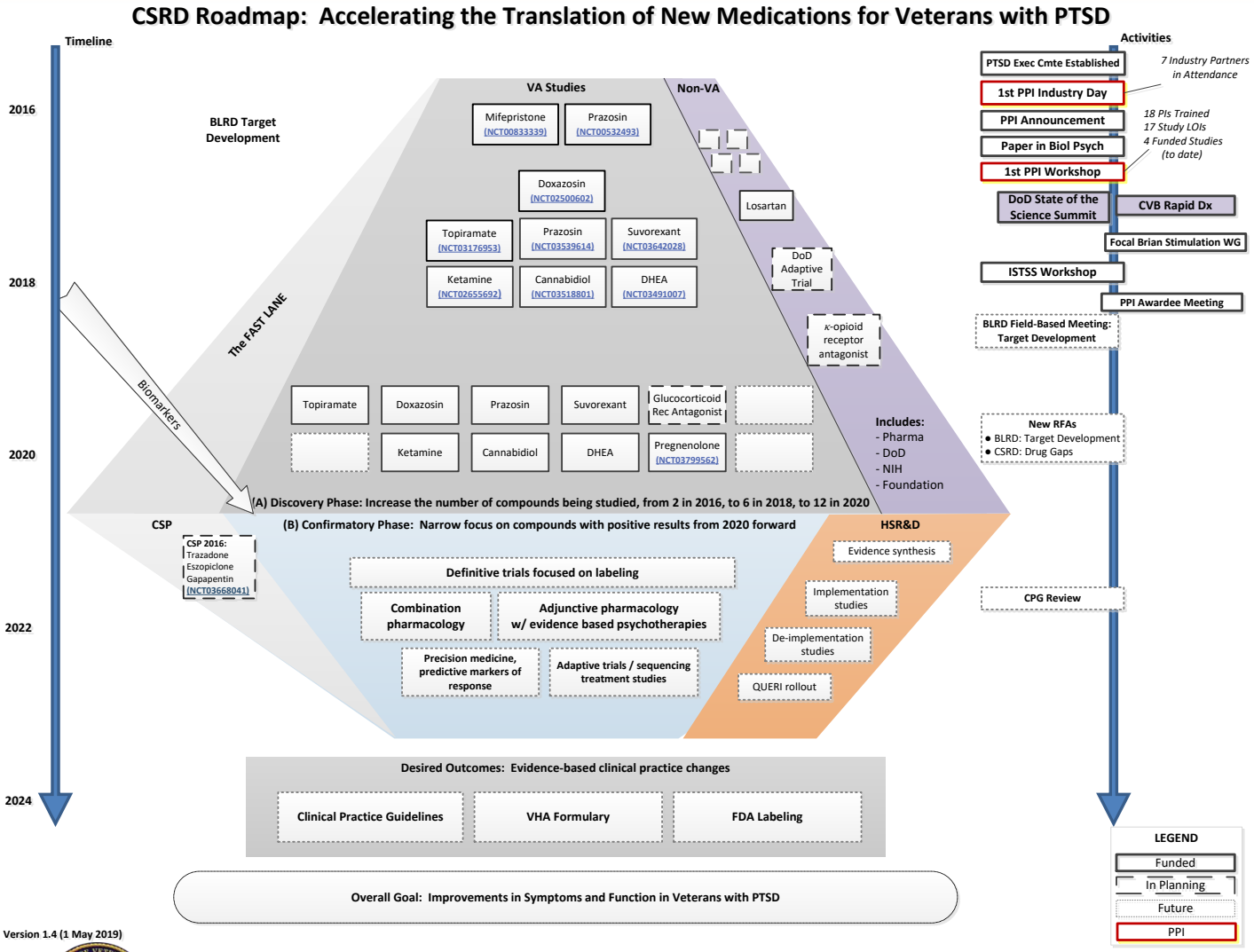
PPI ACCOMPLISHMENTS (2)

- Focused outreach to other funding agencies to coordinate efforts on this topic
- Increased the number of recruitment sites for trials
- Participated in Research Day on Capitol Hill, 2018
- VA/DoD developed 3rd Edition of PTSD Clinical Practice Guidelines, Version 3.0 released July 2017
- Recent "satellite" efforts launched:
  - Focal brain stimulation device working group
  - BLRD field based meeting (2019) of funded applicants; focus on identifying new targets (long-term) and animal models for preclinical study
- Developed a Roadmap to plan and execute PPI series of trials

PPI - LONGER-TERM GOALS

- Large-scale public/private partnership to accelerate understanding of the biology of PTSD and to facilitate the development of novel drug treatments for PTSD
- Reliable and valid biomarkers to aid in predicting who will develop PTSD, diagnosing PTSD, predicting treatment outcome and measuring treatment response
- Strategies to enhance the effectiveness of existing treatments including in partial responders and develop more effective treatments
- Collaboration across studies for data collection, data sharing
- DOD - adaptive platform trial for PTSD medications

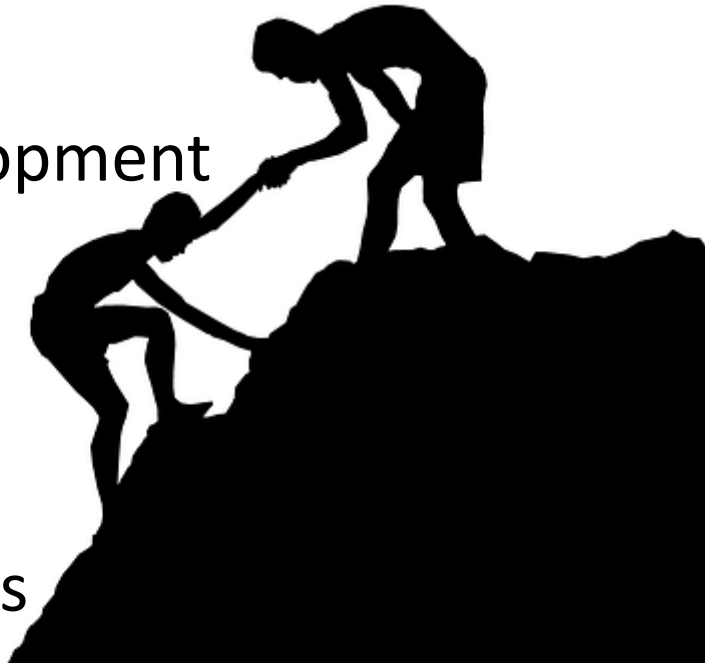
PPI Roadmap


CSRD Roadmap: Accelerating the Translation of New Medications for Veterans with PTSD
Timeline
2016
2018
2020
2022
2024
BLRD Target Development
VA Studies
Non-VA
Mifepristone (NCT00833339)
Prazosin (NCT00532493)
Doxazosin (NCT02500602)
Topiramate (NCT03176953)
Prazosin (NCT03539614)
Suvorexant (NCT03642028)
Ketamine (NCT02655692)
Cannabidiol (NCT03518801)
DHEA (NCT03491007)
Losartan
DoD Adaptive Trial
κ-opioid receptor antagonist
Topiramate
Doxazosin
Prazosin
Suvorexant
Glucocorticoid Rec Antagonist
Ketamine
Cannabidiol
DHEA
Pregnenolone (NCT03799562)
The FAST LANE
Biomarkers
Includes:
- Pharma
- DoD
- NIH
- Foundation
(A) Discovery Phase: Increase the number of compounds being studied, from 2 in 2016, to 6 in 2018, to 12 in 2020
(B) Confirmatory Phase: Narrow focus on compounds with positive results from 2020 forward
CSP
CSP 2016: Trazadone Eszopiclone Gapapentin (NCT03668041)
HSR&D
Evidence synthesis
Implementation studies
De-implementation studies
QUERI rollout
Definitive trials focused on labeling
Combination pharmacology
Adjunctive pharmacology w/ evidence based psychotherapies
Precision medicine, predictive markers of response
Adaptive trials / sequencing treatment studies
Desired Outcomes: Evidence-based clinical practice changes
Clinical Practice Guidelines
VHA Formulary
FDA Labeling
Overall Goal: Improvements in Symptoms and Function in Veterans with PTSD
Activities
PTSD Exec Cmte Established
7 Industry Partners in Attendance
1st PPI Industry Day
PPI Announcement
18 PIs Trained
17 Study LOIs
4 Funded Studies (to date)
Paper in Biol Psych
1st PPI Workshop
DoD State of the Science Summit
CVB Rapid Dx
Focal Brian Stimulation WG
ISTSS Workshop
PPI Awardee Meeting
BLRD Field-Based Meeting: Target Development
New RFAs
• BLRD: Target Development
• CSRD: Drug Gaps
CPG Review
LEGEND
Funded
In Planning
Future
PPI
Version 1.4 (1 May 2019)

How to Collaborate with VA

POSSIBLE PARTNERS

- **Partners internal to VA**
  - VA intramural scientists
  - VA Office of Research and Development



- **Partners external to VA**
  - Commercial partners
  - Federal/interagency partnerships
  - Other: Foundations/scientific associations

Success Stories with Commercial Partners

- **Vaccine development:** Shingles vaccine (Zostavax) - VA and Merck partnered in this large clinical trial which established clinical standard in healthcare
- Rheumatoid arthritis drug Methotrexate - partnership between VA and Amgen described **therapeutic regimen for RA**
- PTSD trial with the drug risperidone **changed prescribing practice** via collaboration with Janssen
- Deep brain stimulation **device partnership** with Medtronics and NINDS shows benefit for Parkinson's disease patients

Funding "Pathways" with Partners

- Internal/intramural VA research funds only – VA investigator proposes a research study and submits for VA peer review with complete funding support from ORD
- External funds only – commercial entity works directly with VA non-profit corporation (NPC), affiliated with local VA Medical Center
- Combination: intramural funding and "in kind" activity or donation/corporate funding + VA funding

WHO do I contact if I'm an external partner?

- **Local** VA collaborations may be developed directly with a VA intramural scientist, who will work with the local facility to ensure proper execution and implementation
- **National** collaborations may be initiated with a VA intramural scientist or partners may contact the VA Office of Research & Development directly. Examples include large multisite studies, interagency activities, and national scientific foundations/associations

Some Tools of the Trade

- **Cooperative research and development agreement (CRADA):** documents the collaborative work to be conducted between the VA and non-federal partners (i.e. commercial). Model CRADAs are available from VA Research. Master CRADAs are also possible. NPC can lead in CRADA development and support management of non-federal partner funding.
- **National Association of Veterans' Research and Education Foundation (NAVREF):** also supports multi-site VA research commercial partnerships: http://www.navref.org/

A private company wants to partner with VA research…

- **If using their own funding**, partners reach out to intramural scientists, and/or NPCs at VA Medical Center(s) directly
- **If seeking funding from VA ORD**:
  - Both partners need to describe what resources are available and what is needed from the other
  - PI must be an eligible VA scientist
  - Application must be submitted by local R&D office in response to a published Request for Applications (RFA)
  - Application is reviewed and evaluated for scientific merit, feasibility, and relevance to the Veteran population to determine whether VA research funding will support the study
  - ORD communicates directly with the VA intramural scientist regarding the application, but also may work with the private partner to identify additional potential VA collaborators.

Partnering Resources

- Central Office Resources:
  - VA Office of Research & Development
  - VA Research Technology Transfer Program
- Local VAMC Resources:
  - VA Medical Center Research Offices
  - VA Medical Center Non-profit Corporations
- VA intramural scientists interested in scientific collaboration (Find currently funded investigators by visiting NIH RePORTER and selecting VA for Agency/Institute/Center)

Letter of Intent

- Submission of a clinical trial requires an approved Letter of Intent
  - Deadlines: May 1 (Fall), November 1 (Spring)

- Information detailed in LOI:
  - Focus (critically important disease, sole focus)
  - Design (sufficient sample size, clinically meaningful outcome measure, rationale, feasibility)
  - Cover Page, Template, Biosketch, FDA documentation (if applicable)
  - Waivers (if applicable)

Dissemination/Implementation of Research Results

Congratulations on successfully testing your PTSD intervention!

… Now what?

ORD Supports Implementation Science

- A rich environment within Health Services is primed to move scientific evidence forward into healthcare, an ultimate goal for VA research
- We work closely with VA clinical program offices to coordinate rollout and dissemination activities, including research to guide the most effective implementation
- Large scale efforts such as definitive clinical trials plan implementation strategies along with the study to be prepared for implementation into healthcare system

May 2019 Message

- VA has a large investment is psychopharmacology, with PTSD Psychopharmacology Initiative one exemplar that includes a roadmapped strategy
- Translation of research findings towards advancing healthcare is a major emphasis and should be considered early and at every stage of VA funded research
- Enterprise-wide collaboration is needed to establish the strongest evidence for new treatments
- We welcome discussion with all potential partners

Questions???

Within VA, work with your local VA medical center research office

Address email to: Theresa.Gleason@va.gov