Study Title	Minocycline for Treatment of Posttraumatic Stress Disorder in Veterans
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Background:

Posttraumatic Stress Disorder (PTSD) is a debilitating disorder characterized by re-experiencing aspects of the original trauma, avoidance and numbing of trauma reminders, and general hyperarousal. Lifetime prevalence of PTSD in community samples is around 6.8%, Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF) veterans around 12.5%, and as high as 30% among Vietnam veterans.[1,2] According to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), one must experience a specific set of symptoms for at least one month following exposure to a traumatic event in order to meet criteria for PTSD.

It has been proposed that cumulative stress may play a significant role in the development of PTSD.[3] There is also evidence that impairments in higher-order cognitive abilities (i.e., executive functions) may contribute to symptoms of PTSD.[4,5] One possibility is that chronic inflammation may contribute to PTSD symptoms. Several studies have reported elevated levels of pro-inflammatory cytokines such as C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNFα) in patients with PTSD. Groer et al. studied levels of inflammation in active duty military personnel and found that elevated CRP was associated with depression and PTSD symptoms.[6] Another study that compared two groups of combat exposed veterans, one group with PTSD and one without, found that combat-related PTSD in males was associated with higher levels of pro-inflammatory cytokines, even after accounting for depression.[7] It has been proposed that elevated inflammatory cytokine activity in individuals with PTSD may result from inadequate regulation by the stress hormone cortisol.[8] Low levels of cortisol promote excessive catecholamine production, which can lead to enhanced sympathetic activity. Enhanced sympathetic activity can amplify traumatic memories and lead to expression of PTSD symptoms.[9] These findings indicate that increased inflammation due to disruption of the HPA axis and altered immune system feedback may play a role in the development of PTSD.[10] Furthermore, in a recent prospective study, Eraly et al. examined levels of CRP in active-duty military personnel 3-6 months after returning from deployment. They found that those with elevated pre-deployment levels of CRP were more likely to develop PTSD, suggesting that individuals with higher inflammation may be more likely to develop PTSD.[11]

Such findings raise the possibility that inflammation may serve as a potential target for treatment in individuals with PTSD. Minocycline is a broad-spectrum tetracycline antibiotic with anti-inflammatory and neuroprotective properties and has been shown to

reduce levels of pro-inflammatory cytokines. Several studies have reported evidence indicating that minocycline may help in treating symptoms of psychiatric disorders such as schizophrenia[12-17] and depression.[18,19] Such treatments might also prove beneficial in treating health conditions associated with chronic inflammation that are commonly comorbid with PTSD, such as chronic pain, arthritis, diabetes, and cardiovascular disease.[8,20] A study using an animal model of PTSD found a reduction in stress-related behaviors as well as decreased levels of inflammatory cytokines, suggesting that the anti-inflammatory effects of minocycline may help to improve symptoms of PTSD.[21] In addition, a recent study of fear conditioning in humans found attenuated fear memory in individuals administered the tetracycline antibiotic doxycycline, suggesting that such medications may help to improve symptoms of PTSD.[22] However, no studies to date have investigated the efficacy of minocycline treatment in veterans with PTSD.

Significance:

The Veterans Health Administration has a growing population of veterans exposed to combat during their military service, and there is a clear need to identify more effective forms of treatment for PTSD. Understanding the clinical phenomenology, risk factors and potential biomarkers of this condition could pave the way for better screening methods and treatment interventions for clinicians.

Study Aim:

The specific aim of this pilot study is to assess the safety and efficacy of adjunctive minocycline treatment in veterans with PTSD.

Hypothesis:

We hypothesize that treatment with adjunctive minocycline will be associated with reduced inflammation (as indexed by levels of inflammatory cytokines) and reduced severity of PTSD and mood symptoms.

Study Design:

A 12-week, open-label pilot study in which adjunctive minocycline will be administered to approximately 15 subjects diagnosed with PTSD.

Participants:

Recruitment: Participants will be recruited from the pool of patients presenting to the Omaha VA Medical Center.

Inclusion Criteria:

1. Veterans between the ages of 19 and 65 who meet DSM-5 criteria for chronic PTSD.
2. Patients who have been taking an adequate dose of SSRI or SNRI medication, bupropion, or mirtazapine for a minimum of 8 weeks at the time of study entry.
3. PTSD Checklist for DSM-5 (PCL-5) score of $\geq$ 33 at the Screening Visit. Eligible persons will be allowed to have other symptoms that are commonly comorbid with PTSD (e.g., anxiety, somatic symptoms). This strategy will provide a feasible and generalizable sample of those with chronic PTSD.

Exclusion Criteria:

1. Patients with a concurrent DSM-5 diagnosis in any of the following categories:
   1.1. Major Neurocognitive Disorder (NCD)
   1.2. Lifetime Schizophrenia and other Psychotic Disorders
   1.3. Lifetime Bipolar Disorder
   1.4. Alcohol Dependence or Abuse in 3 months prior to the Screening Visit
   1.5. Any other Substance Dependence or Abuse (excluding nicotine) in 12 months prior to the Screening Visit
   1.6. Any other concurrent Axis I Disorder (including Major Depressive Disorder) must be secondary to the primary diagnosis of PTSD.
2. Chronic pain levels requiring use of any opiate medications with the exception of Tramadol. Patients are allowed the use of Tramadol at 25-50 mg per day dosing.
3. Any condition or disorder that may cause neuropsychiatric sequelae (e.g., Parkinson's disease, stroke, seizures, or TBI).
4. Past chronic PTSD, meaning PTSD that preceded the incident traumatic event responsible for the current PTSD. Other traumatic life events will not be exclusionary unless they resulted in previous PTSD.
5. Patients with a history of intolerance or hypersensitivity to minocycline or other tetracycline antibiotics, or prior tetracycline use 2 months prior to the Screening Visit.
6. Concomitant treatment with penicillin or other antibiotics, or treatment with antibiotics for greater than 7 days in the past month.
7. Use of aspirin, non-steroidal anti-inflammatory agents (NSAIDs) or COX-2 inhibitors for < 6 months prior to study entry or dose changes after study entry. Limited as-needed use is permitted prior to study entry but not during the study.
8. Use of statins will not be permitted during the study as they have been shown to reduce levels of pro-inflammatory cytokines.
9. Use of concomitant anti-coagulant drugs (except low-dose aspirin) as minocycline has been shown to depress plasma prothrombin activity.
10. Any degree of hepatic or renal failure that in the Investigator's judgement would pose a safety risk for treatment with minocycline. There are no dosage adjustments recommended in the manufacturer's labeling in hepatic insufficiency. In case of renal

impairment the following PDR guidelines will be followed: CrCl ≥80 mL/minute: No dosage adjustment necessary; CrCl <80 mL/minute: Do not exceed 200 mg daily.

11. Conditions which may be negatively affected by minocycline treatment, such as active inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease).
12. A history of C. difficile colitis.
13. Patients who based on history or mental status examination have a significant risk of committing suicide, or who are homicidal or violent and who are in the Investigator's opinion in significant imminent risk of hurting others.
14. Patients who have a medical condition that, in the Investigator's opinion, would expose them to an increased risk of a significant adverse event or interfere with assessments of safety and efficacy during the course of the trial.
15. Women who are pregnant or plan to become pregnant during the study. All women of childbearing potential must have a negative urine pregnancy test at the Screening Visit and throughout the study. Sexually active women participating in the study must use a medically acceptable form of contraception.
16. Patients with a current known infection or who are acutely ill.
17. Patients with an autoimmune disease (i.e., Lupus, Rheumatoid Arthritis).
18. Immunocompromised patients (i.e., HIV).
19. Patients with thyroid disorders unless euthyroid at screening.
20. Patients with cancer not in remission.
21. Patients with CVD, such as myocardial infarction and arrhythmias.
22. Patients with diabetes.
23. History of significant esophagitis.
24. Patients who plan to initiate or terminate any psychotropic medication during the study. Patients taking any psychotropic medication should be on a stable dose for at least 6 weeks prior to the Screening Visit (except for the SSRI, SNRI or mirtazapine used to treat their PTSD) AND agree not to discontinue or otherwise alter treatment during the study.
25. Patients who plan to initiate or terminate any form of psychotherapy or behavior therapy during the study with the exception of PTSD Orientation Group. Subjects may be in supportive psychotherapy if it was initiated at least three months prior to the Screening Visit AND subject agrees not to discontinue or otherwise alter therapy during the study. Subjects receiving evidence-based psychotherapies such as Prolonged Exposure or Cognitive Processing Therapy will be excluded.
26. Patients who are unable to speak, read, and understand English or are judged by the Investigator to be unable or unlikely to follow the study protocol and complete all scheduled visits.

Study Procedures:

The schedule of all study visits and procedures is summarized below and in Table 1.

Screening Visit (Visit 1):

After providing informed consent, patients will be screened for participation in the study. The Mini-International Neuropsychiatric Interview (MINI) will be used to screen for comorbid psychiatric disorders. The PTSD Checklist for DSM-5 (PCL-5) will be used to confirm diagnosis of PTSD. Depression symptoms will be assessed using the Beck Depression Inventory-II (BDI-II). Medical history, physical exam, vital signs, and review of concomitant medications will also be completed.

Blood and urine samples will be obtained and tested by the Omaha VA Outpatient Lab. Laboratory tests will include complete blood count (CBC), comprehensive metabolic panel (CMP), routine urinalysis, urine pregnancy test (if applicable), C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNFα). Based on previous research, we anticipate that levels of pro-inflammatory cytokines (CRP, IL-6, and TNFα) may be elevated. However, as patients with non-elevated cytokine levels at screening may still exhibit significant change over the course of the study and provide useful data, no minimum cutoff level for cytokines will be used in this study.

Baseline Visit (Visit 2):

PTSD symptoms will be assessed using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). The CAPS is a 30-item structured interview that corresponds to the DSM criteria for PTSD. It is considered by many to the gold standard in the diagnosis and assessment of PTSD. We will use the CAPS to assess past month (current) PTSD. The Clinical Global Impressions (CGI) Scale will be administered to assess overall severity of symptoms, and vital signs will also be obtained. As previous research indicates that executive dysfunction may contribute to PTSD symptoms,[4,5] we will assess executive functioning using two measures: the Trail Making Test (TMT) and Controlled Oral Word Association (COWA) Test. The TMT is a measure of visual attention and task switching, while the COWA is a measure of verbal fluency. Concomitant medications will be reviewed and drug dispensing will occur at this visit.

Follow-up Visits (Visits 3-6):

Visit 3 will be a telephone contact to monitor dose increase from 100mg/day to 200mg/day. Visits 4-6 will be clinic visits to include the following procedures: vital signs, adverse event evaluation, drug dispensing/accountability/adjustment, and review of

concomitant medications. The CGI will be administered to assess overall severity and improvement in symptoms.

End of Study (Visit 7):

The end of study visit will include administration of the CAPS, BDI-II, CGI, TMT, and COWA scales, as well as physical exam, vital signs, and laboratory evaluation (including measurement of CRP, IL-6, and TNFα). Adverse event evaluation, drug accountability, and review of concomitant medications will also be completed at this visit.

Safety Follow-up (Visit 8):

This visit will be conducted only for patients who have ongoing adverse event(s). The following procedures will be completed at this visit: CGI, vital signs, adverse event evaluation, and review of concomitant medications.

Study Medication and Dosing Regimen:

This is a 12-week, open-label study in which minocycline will be administered to veterans with PTSD. Dosing will be titrated to reduce potential side effects that may be experienced when starting minocycline. The titration schedule is as follows: 100 mg/day 1 to 7, 200 mg/day 8 to end of week 12.

During the course of the study patients will be supplied with 100 mg minocycline capsules. Study medication will be administered as a single daily dose (100 mg total/day 1 to 7) or twice daily dose (200 mg total/day 8 to end of week 12). Subjects will be instructed to take study mediation with a full glass of water and to not lie down for at least 30 minutes after taking it. Also, patients taking antacids containing aluminum, calcium, or magnesium and preparations containing iron will be instructed to take these at least 2 hours before or after minocycline administration.

The Investigator may adjust the dosing regimen during the course of the study based on tolerance to the study medication. The maximum dose permitted for minocycline will be 200 mg per day. Upon the Investigator's determination of the dosage regimen for each subject, the study medication will be dispensed in an amount sufficient to cover the window between the study visits plus at least 3 extra days during the first month of the trial, and 7 days over the second and third months.

Treatment compliance will be monitored by counts of returned medication. Records of concomitant medications will be taken at each study visit as well as reports of adverse events.

Efficacy Evaluation:

The primary efficacy measures will be (1) change in CAPS total scores from baseline to end of study, and (2) change in levels of the inflammatory cytokines CRP, IL-6, and TNF-α from screening to end of study. Secondary measures of efficacy will include change in BDI-II, CGI, TMT, and COWA scores from baseline to end of study.

Statistical Analysis:

Statistical analyses will include t-tests (or a nonparametric equivalent) for comparison of scores on CAPS, BDI-II, CGI, TMT, and COWA from baseline to end of study and change in inflammatory cytokine levels from screening to end of study. Correlational analyses will be used when appropriate to determine the degree of association among variables. Further analyses will be conducted to examine the effects of other factors on the primary measures (e.g., medical and psychiatric history, concurrent psychiatric treatment). SPSS software will be used for statistical analyses.

Safety Evaluation and Monitoring:

Safety will be monitored by reports of adverse events at all treatment visits throughout all phases of the study. This may include any clinically significant changes in vital signs (blood pressure, pulse, and weight), physical examinations, laboratory evaluations (blood chemistry, hematology, and urinalysis) and recording of concomitant treatment. In cases of adverse effects of minocycline treatment, trial medication will be stopped for five days and then recommenced. Participants will be contacted following recommencement to determine if adverse effects have returned.

Treatment compliance will be monitored by counts of returned medication, and patients will be counseled if they do not adhere, or if they are thought to be at risk for not adhering to the medication regimen.

A Data Safety Monitoring Committee (DSMC) will be utilized to ensure patient safety and will consist of expert clinicians in the disease area. Drs. Robert Langenfeld and Angelo Zieno, Staff Psychiatrists will review safety data. The DSMC will have access to any and all data to assess the safety of the subjects. Adverse event data will be tallied and maintained for the DSMC to review. Following each data review, the DSMC will make recommendations regarding the conduct of the study, including continuing the study without modifications, to terminate or to modify the study design for safety reasons.

The following will be considered as decision rules to discontinue the subject's participation in the study: If the subject develops symptoms requiring treatment with

antibiotics or other forms of treatment not permitted during the course of the study (see Exclusion Criteria). If the subject experiences a serious adverse event. If the subject develops suicidal or homicidal thoughts. If the subject misses two or more consecutive study visits in a row. If the subject takes less than 80% of the study medication as prescribed.

Human Subject Protection and Confidentiality:

During screening, we anticipate some subjects to endorse suicidal thoughts either current or past. We propose to manage suicide risk by a systematic and careful assessment of suicidality. Subjects will be assessed at screening using the MINI Suicidality Module. This instrument provides information regarding past history of suicidal ideation and attempts as well as information about recent and current suicidal thinking, plans and attempts. Participants with a past history of attempt(s) and/or current serious ideation will trigger a more detailed review of their risk by the PI. The disposition of subjects with serious symptoms will follow standard clinical care protocol. Such subjects will not proceed in the study.

Patients with diagnosis of major mental disorders (e.g., bipolar disorder, psychotic disorders) that were previously undiagnosed will be referred to the PCP for further management and will be offered a same day walk-in appointment in the Mental Health Clinic.

Utmost care will be taken to ensure subjects' psychological well-being and minimize discomfort during administration of protocol assessments. Psychological instruments will be administered by team members trained and experienced in dealing with PTSD. In the event a subject experiences worsening mood, anxiety or sleep problems following the visits, they will be provided an opportunity for debriefing and may exit the study if they require treatments not permitted during the study.

To protect privacy and confidentiality, we used only coded data without patient names or identifiers. All working papers will be stored in a secure area and will be shredded when they are no longer useful. An electronic database will be created for storage of the data. Data from all sources will be entered into an Excel spreadsheet maintained in a secure, limited access folder on the secure VA NWI server via secure VA computers directly on site. De-identified data in the Excel spreadsheet eventually would be converted into a SPSS database for statistical analysis. No PHI or other identifiable data will leave the VA secure environments, physical or electronic. Access to the records will be limited to the study team.

All participants will be asked to sign a HIPAA authorization to allow for access and use of protected health information (PHI). This authorization will expire at the end of the study. Protected health information (PHI) to be used or collected will include information from patients' VA Health Records (e.g., diagnoses, medications) and specific information concerning alcohol and drug abuse, HIV, demographics, and questionnaires. This information may be disclosed to entities outside the VA, including other federal agencies required to monitor or oversee research (e.g., the Food and Drug Administration (FDA), Government Accounting Office (GAO), Office of Human Research Protection (OHRP)), Nebraska Educational Biomedical Research Association (NEBRA), and a VA contractor for purposes of accreditation.

Resources:

No resources beyond what is already available in terms of staff and equipment will be necessary to conduct this project.

Source of Funding:

NEBRA - Nebraska Educational Biomedical Research Association, Creighton University

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Table 1. Study Visit Schedule

Trial Phase	Screening	Baseline	Follow-up Visits				End of Study or ET	Safety Follow-up**
Visit #	**V1**	**V2**	**V3***	**V4**	**V5**	**V6**	**V7**	**V8**
End of Week #	**-1**	**0**	**1**	**2**	**4**	**8**	**12**	**13**
Informed Consent	x							
Eligibility Criteria	x							
Clinical Evaluation								
PCL-5	x							
MINI	x							
CAPS		x					x	
BDI-II	x						x	
CGI		x		x	x	x	x	x
TMT		x					x	
COWA		x					x	
Medical Evaluation								
Medical History	x							
Physical Exam	x						x	
Vital Signs	x	x		x	x	x	x	x
Lab Procedures								
Blood Draw	x						x	
Complete Blood Count (CBC)	x							
Comprehensive Metabolic Panel (CMP)	x							
Urinalysis	x							
Urine Pregnancy Test	x							
C-reactive protein (CRP)	x						x	
Interleukin 6 (IL-6)	x						x	
Tumor necrosis factor alpha (TNFα)	x						x	
Safety								
AE Records			x	x	x	x	x	x
Other								
Drug Dispense/Account/Adjust		x		x	x	x	x	
Con Meds	x	x		x	x	x	x	x
Patient Stipend	x	x		x	x	x	x	x

* Telephone visit, ** The safety follow-up visit will be conducted only for patients with ongoing adverse events.