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TITLE: Evaluation of Multiple Potential Pharmacogenomic Risk Factors for Chronic Mefloquine Neurotoxicity through the Establishment of a Drug Safety Registry

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CONTRACTING ORGANIZATION: Uniformed Services University
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Bethesda, MD 20814

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5b. GRANT NUMBER
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5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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Clinical Research Unit, BLDG 53, Dept of Medicine
Bethesda, MD 20814

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9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Development Command (USAMRDC)
Fort Detrick, Maryland 21702-5012

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12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
The purpose of this study is to investigate possible pharmacogenomic risk factors for mefloquine neurotoxicity and potentially find markers that may differentiate between mefloquine toxicity and PTSD. This study is a pilot study powered to find large, clinically significant differences in genetic variants along with exploratory objectives aimed at looking for trends in symptom complexes, environmental interactions with various genetic markers and differences between mefloquine toxicity and PTSD. The subject population includes anyone with a mefloquine exposure history or diagnosis of PTSD without mefloquine exposure. The study is a cross-sectional case-control study. The protocol has been approved by the USUHS IRB and the business contract is currently being reviewed.

15. SUBJECT TERMS
mefloquine, PTSD, pharmacogenomics, drug adverse events

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			Thomas G. Oliver, COL, MC, USA
U	U	U	UU	7	**19b. TELEPHONE NUMBER** *(include area code)* (301) 295-0016

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Table of Contents

1. INTRODUCTION

The purpose of this study is to investigate possible pharmacogenomic risk factors for mefloquine neurotoxicity and potentially find markers that may differentiate between mefloquine toxicity and PTSD. This study is a pilot study powered to find large, clinically significant differences in genetic variants along with exploratory objectives aimed at looking for trends in symptom complexes, environmental interactions with various genetic markers and differences between mefloquine toxicity and PTSD. The subject population includes anyone with a mefloquine exposure history or diagnosis of PTSD without mefloquine exposure. The study is a cross-sectional case-control study of three groups (1) exposure to mefloquine and had, or continue to have, neuropsychiatric symptoms after exposure (100 subjects), 2) exposure to mefloquine and had no neuropsychiatric symptoms (100 subjects) or 3) had no mefloquine exposure and have a diagnosis of PTSD (50 subject). Subjects will be consented and screened at the Uniformed Services University (USU) Clinical Trials Unit. Once enrolled, subjects will provide a pertinent medical history and if available, have medical records reviewed. They will also complete various validated neuropsychiatric assessments, which are components of the validated NIH Toolbox. Subjects will then have blood drawn for the pharmacogenomic testing, which will be stored in a freezer in BLDG 53 and then be batch analyzed by the TAGC genomic testing laboratory at USU targeting genetic variants of the following genes identified in the medical literature: Alpha-one acid glycoprotein, MDR1, MTHFR, Pyk2, 5HT2a, ADA, A2A, CYP3A4.

2. KEYWORDS

Mefloquine, drug toxicity, pharmacogenomics, neurotoxicity, clinical pharmacology

3. ACCOMPLISHMENTS

What were the major goals of the project? (Goals to be accomplished and status.)

Specific Aim 1: Determine if there is a single or pattern of genomic risk factors for patients who develop mefloquine neuropsychiatric toxicity

Specific Aim 2: Determine if there is a pharmacogenetic risk factor for developing chronic (>6 months) mefloquine neurotoxicity

Specific Aim 3: Determine if there is a relationship between mefloquine toxicity and development of post-traumatic stress disorder (PTSD) with an emphasis on pharmacogenomic risk factors

Specific Aim 4: Determine if there is a way to distinguish between subjects with chronic mefloquine neurotoxicity and subjects with PTSD

Major Task 1: Prepare Research Case Control Protocol (months 1-8) – 100% complete

Major Task 2: Coordinate Study Staff for Study (month 7) – 100% complete

Major Task 3: Clinical Study (months 8-30) – 15% complete

Major Task 4: Genotyping of various genes (months 6-32) – 0% complete

Major Task 5: Data Analysis (months 32-36) – 0% complete

What was accomplished under these goals? (Detailed progress and results.)

All research at USU which is not related to COVID-19 was put on hold shortly after the reported period opened. There was minimal progress made on the study. We screened 5 subjects but did not enroll anyone. A no-cost extension for 1 year was approved. We are hoping to be able to resume the study in July or August 2020. Enrollment for the study remains on hold. To date, 33 subjects have been enrolled, goal 250 subjects.

What opportunities for training and professional development has the project provided?

Nothing to report

How were the results disseminated to communities of interest?

Nothing to report

Plans for the next reporting period to accomplish the goals

USU is beginning Phase 2 of the reopening process and may allow a partial resumption of non-COVID research. The IRB has been petitioned for a clarification of the return to work procedures and authorization to resume recruitment.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

USU has put a moratorium on non-COVID related research and it has yet to be rescinded. To mitigate this we have asked for and received a 1 year no cost extension. It is our intention to complete the study during the allotted time, should research be allowed to resume.

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects

TOTAL PROTOCOL(S): 1

IRB Protocol Number: MED-83-9137 (MED-93-9137)
HRPO Protocol Number: Exempt
Protocol PI: Thomas Oliver
Protocol Site: USU

Protocol Title: Evaluation of Multiple Potential Pharmacogenomic Risk Factors for Chronic Mefloquine Neurotoxicity through the Establishment of a Drug Safety Registry
Target approved for clinical significance: 250 subjects
IRB INITIAL APPROVAL DATE: 01/11/2019
HRPO INITIAL APPROVAL DATE: 04/14/2017 (HRPO determined exempt from review b/c research is at DOD lab)
CONTINUING REVIEWS APPROVAL DATES:

- 01/17/2019 (expires 02/01/2020)
- 01/10/2020 (expires 02/01/2021)

AMENDMENTS:

- 2019-07-30, USUHS IRB approved adding Dr. Joshua Gray, Psychologist to the study (ref# 916373)
- 2019-12-01, IRB approved to add additional tests and reduce dose from 4 to 1(Amendment ref# 921389)
- 2020-01-14, IRB approval of continuing review, (ref# 922012)

ENROLLMENT STATUS:
Number of subjects recruited/original planned target: 155/250
Number of subjects screened/original planned target: 146/250
Number of patients enrolled/original planned target: 33/250
Number of patients completed/original planned target: 33/250
ADVERSE EVENTS OR UNANTICIPATED PROBLEMS:

- none

Significant changes in use or care of vertebrate animals

No animal use research is involved.

Significant changes in use of biohazards and/or select agents

No biohazard or select agent research is involved.

6. PRODUCTS

Journal publications

Nothing to Report

Books or other non-periodical, one-time publications

Nothing to Report

Other publications, conference papers, and presentations

Nothing to Report

Website(s) or other Internet site(s)

Nothing to Report

Technologies or techniques

Nothing to Report

Inventions, patent applications, and/or licenses

Nothing to Report

Other Products

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	COL Thomas Oliver
Project Role:	PI
Researcher Identifier:	
Nearest person month worked:	2.5
Contribution to Project:	Coordination with protocol amendment modification and submission process. Assisted with neurobehavioral assessment process
Name:	LTC Jeffrey Livezey
Project Role:	AI
Researcher Identifier:	
Nearest person month worked:	2.5
Contribution to Project:	Coordination with protocol amendment modification and submission process. Assisted with neurobehavioral assessment process.
Name:	Dutchabong Shaw, RN, BSN, MA, CCRP
Project Role:	Research Coordinator
Researcher Identifier:	
Nearest person month worked:	4.0
Contribution to Project:	Coordinated neurobehavioral assessment process.
Name:	Joshua Gray, PhD
Project Role:	Clinical Psychologist
Researcher Identifier:	
Nearest person month worked:	1.0
Contribution to Project:	Reviewed and modified the neurobehavioral test battery.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHART

Convert this report to a PDF file and append updated quarterly Quad Chart in PDF as an appendix.

9. APPENDICES

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Appendix 1, Quad Chart.

Evaluation of multiple potential pharmacogenomic risk factors for chronic mefloquine neurotoxicity through the establishment of a drug safety registry

Clinical Research Initiative - Precision Medicine Research Award

DM160475

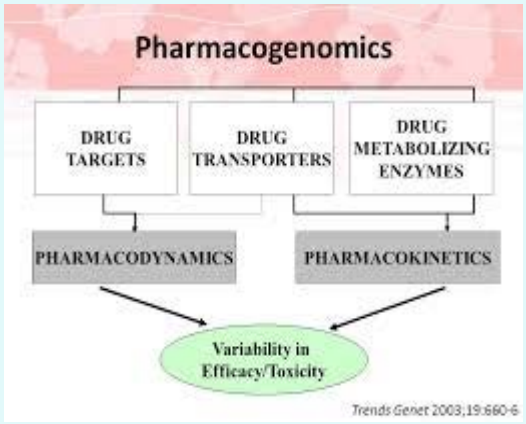
PI: COL Thomas Oliver MD **Org:** Uniformed Services University **Award Amount:** $319,000

Study/Product Aim(s)

- Determine if there is a single or pattern of genomic risk factors for patients who develop mefloquine neuropsychiatric toxicity
- Determine if there is a pharmacogenetic risk factor for developing chronic (>6 months) mefloquine neurotoxicity
- Determine if there is a relationship between mefloquine toxicity and development of post-traumatic stress disorder (PTSD) with an emphasis on pharmacogenomic risk factors.
- Determine if there is a way to distinguish between subjects with chronic mefloquine neurotoxicity and subjects with PTSD

Approach

Perform a case control study of subjects who have reported neuropsychiatric toxicity after exposure to mefloquine. Data to be collected include medical history, neuropsychiatric evaluation and genetic variants of genes involved in mefloquine PK and PD.



Explaining the toxicity of mefloquine in service members through pharmacogenomics

Timeline and Cost

Activities CY	18	19	20	21
Study & Protocol Development				
Conduct Clinical Study				
Finish study and Data Analyses				
Estimated Budget ($K)	**$**	**$20**	**$100**	**$125**

Updated: 09 JUL 2020

Goals/Milestones

CY18 Goals – Study and Protocol Development

X Complete and obtain IRB approval of clinical protocol

X Add Clinical Psychologist to the study staff and amend the protocol to reflect the most current neurobehavioral testing.

CY19 Goal – Clinical Study

X Begin screening and enrollment for the case control study

CY20 Goal – Clinical study

X Continue case control study. Obtain NCE

CY21 Goal – Complete clinical study

☐ Enroll & complete case control study/data analysis 250 subjects

Comments/Challenges/Issues/Concerns

- Enrollment:
- Chronic mefloquine toxicity-slow
- All other groups-acceptable rate

Budget Expenditure to Date

Projected Expenditure: $260,000

Actual Expenditure: $27,000