Non-intrusive Detection of Temporary Neurologic Impairment By Opioids

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Non-intrusive Detection of Temporary Neurologic Impairment By Opioids

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Study Product: Oxycodone (Immediate Release)

Protocol Number: (IRBe) 19-004883

Initial version: 7/1/2019 Version **(1.0)**
Follow Up Version: 11/01/2021 Version (2.0)

List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure

Study Summary

Title	Non-intrusive detection of temporary neurologic impairment by opioids
Protocol Number	19-004883
Phase	1
Methodology	Screening and Evaluation procedure for Oxycodone
Overall Study Duration	One year
Subject Participation Duration	Visits: 3 Time per visit: 3-4 hours
Single or Multi-Site	Single site
Objectives	The overall goal is to establish an understanding of the physiologic effects of opioid use on oculomotor dynamics, and to identify the presence of unique characteristic changes in these dynamics consistent with this specific drug or class of drugs.
Number of Subjects	25
Diagnosis and Main Inclusion Criteria	Participants must be able to consent to participate themselves Be healthy male or non-pregnant female Be 21 to 59 years of age Must be able to attend in-person sessions at the Mayo Aerospace Medicine and Vestibular Research Laboratory in Scottsdale, AZ. Have not used opioids during the preceding 30 days Must not be in an active pain management program Note: No racial/ethnic groups will be excluded, although all participants must be fluent speakers of English. Minorities and women are included in subject selection, as long as they meet all eligibility criteria. Vulnerable populations are included to ensure that any benefits from future research will be readily available to these populations. To reduce risk, we will confirm that females are non-nursing and non-pregnant, and women must agree to use an effective method of contraception during the study.
Study Product, Dose, Route, Regimen	Oxycodone Immediate Release or Placebo Dose(s): Initial/first dose of 5 mg or placebo, followed by second dose of 5 mg or placebo Dose Route: Oral Dose Regimen: Oxycodone 5 mg or placebo will be administered to subjects followed by a 30 minute rest period to allow for onset of medication effect. This rest period will be followed by oculomotor testing for 40 minutes. After the initial testing, a second dose of oxycodone 5 mg or placebo will be administered followed by a 30

	minute rest period to allow for the onset of the second dose. The second rest period will be followed by a second round of oculomotor testing for 40 minutes.
Duration of Administration	Oxycodone or placebo will be administered only during patient visits 2 and 3.Subjects will be given a total 2 doses of oxycodone or placebo during the aforementioned visits.
Reference therapy	Placebo
Statistical Methodology	Two-way Repeated measures ANOVA (rm-ANOVA) on the eye-tracking features will be implemented to assess the effect of drug (Oxycodone vs. Placebo), amount (high dose vs. low dose) and also the interaction between drugs and amount.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Pain management drugs are widely prescribed and are subject to abuse due to their psychoactive properties. Oxycodone is commonly prescribed for pain which with prolonged use, can lead to addiction. Drug abuse is of great concern to the general public, parents, public health, the medical community, and government. Abuse of legal opioid prescription drugs and subsequent addiction may be associated with the use of illegal drugs such as heroin and fentanyl.

Research previously sponsored by Zxerex Corporation has resulted in the identification of a unique set of changes of oculomotor dynamics consistent with the physiologic effects of marijuana (THC) on the central nervous system. The goal is to establish an understanding of the physiologic effects of opioid use on oculomotor dynamics. As with Marijuana, Zxerex is developing other biosignatures indicative of drug use to be used in a screening tool.

Similar screening procedures, including eye movement analysis, have been applied to other areas of study at the Mayo Aerospace Medicine and Vestibular Research Laboratory (AMVRL).

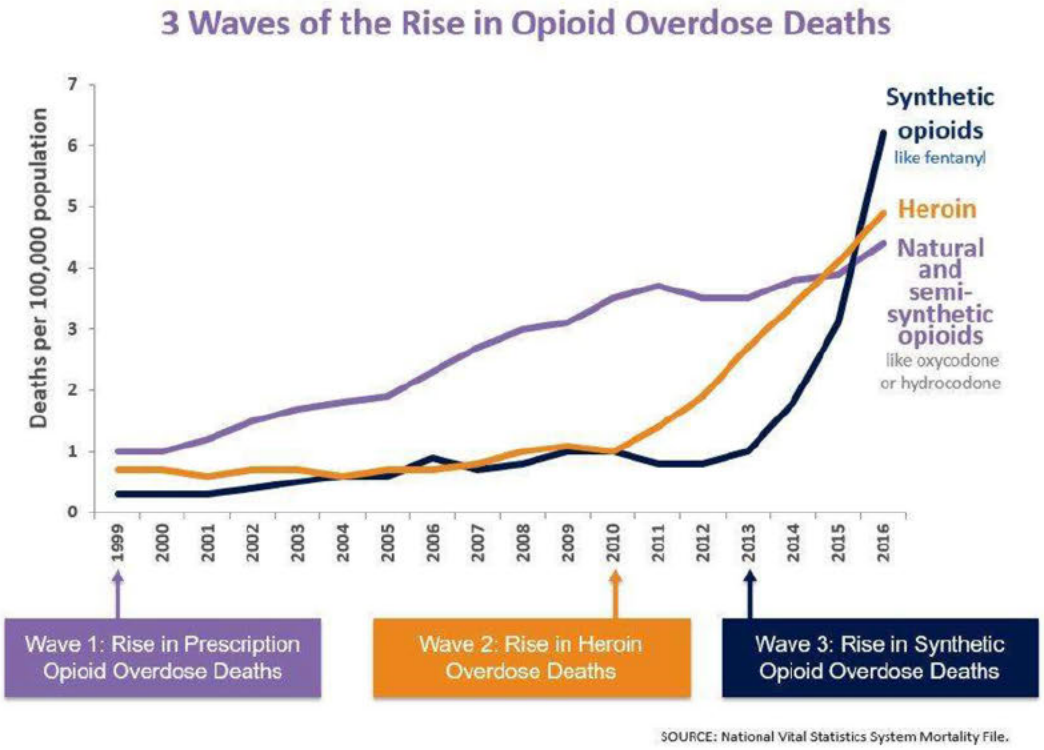
1.2 Drug being studied

Name: Oxycodone (Immediate Release)

Oxycodone is an opioid analgesic that is indicated for use in the management of chronic moderate to severe pain. For this study, immediate release oxycodone 5 mg and matching placebo will be supplied in capsules.

1.3 Clinical Data to Date

According to the U.S. Department of Health and Human Services, Center for Disease Control, 630,000 people have died from drug overdoses between 1999 and 2016, with 66% of the 63,600 drug overdose deaths in 2016 that involved opioids. With 115 people dying every day in the United States from an opioid overdose, this problem has taken on public health connotations and is now referred to as the "opioid epidemic," which is attributed to the use of prescription and illegally acquired opioids and synthetic opioids, such as, fentanyl.



1.4 Dose Rationale

Dosage

Dosing involves an initial dose of 5mg of Oxycodone (Immediate Release), followed by a second dose of 5mg of Oxycodone (Immediate Release) approximately 1.5 hours later. This dose is selected as the represent the commonly prescribed doses of Oxycodone for pain management in opioid naive patients.

Route of Administration

Doses will be administered orally as this is the most common method of administration.

Dose Regimen and Period

Administer drug (5mg), allow 30 minutes to take effect, perform the oculomotor testing (40 minutes), then administer the second dose (5mg), allow 30 minutes to take effect, then perform oculomotor testing (40 minutes).

1.5 Risks and Benefits

Risks that could be encountered during the study period include:

- Drug interaction risks
- During interviews, participants may be asked questions about personal and sensitive matters, which for some may cause stress, or can be upsetting.

Describe procedures for minimizing risks:

- For interviews, participants will be informed in the Consent form about the types of questions they will be asked.

- All participants will undergo medical and clinical evaluations. The results will be communicated to each potential participant, and participants will be consulted and/or referred for further medical and psychiatric attention when warranted.

- Where indicated, we will offer all subjects the option of obtaining help to abstain from drug taking. Subjects requesting treatment prior to the start of the study will be referred to treatment and will not be accepted into the study.

2 Study Objectives

The goal is to establish an understanding of the physiologic effects of opioid use on oculomotor dynamics, and to identify the presence of characteristics changes in these dynamics consistent with a signature of a specific drug or class of drugs.

3 Study Design

This is a two-way repeated-measure study that consists of two independent variables: "Type of drug (Placebo vs. Oxycodone)" and "Amount of drug (Low Dose vs High Dose).

3.1 General Description

This is a screening and evaluation procedure for Oxycodone to be conducted by the AMVRL laboratory at Mayo Clinic, Scottsdale, AZ.

All prospective volunteers will sign a consent form describing the details of the study before the screening process begins.

This screening and evaluation procedure will evaluate the effects of at least two oxycodone doses in subjects who have had prior experience using opioids for pain management.

3.2 Number of Subjects

We project that a minimum of 25 subjects will be required to accomplish the study aims.

3.3 Duration of Participation

Participates will be engaged in three study visits preceded by a telephone interview. The second and third visit (B, C) will occur in a random order.

- Telephone Interview - 20 minutes
- Visit A - 3-4 hours
- Visit B - 3-4 hours
- Visit C - 3-4 hours

3.4 Primary Study Endpoints

The primary study endpoints will be the identification of characteristic physiologic effects of opioid use on oculomotor dynamics, and to identify through data analysis the presence of unique characteristics consistent with the administration of Oxycodone.

3.5 Identification of Source Data

The following source data will be directly recorded on the Case Report Form (CRF):

- Patient Completed Questionnaires

The following source data will not be directly collected in the Case Report Form (CRF), but will be captured in supportive documentation and data files:

- Oculomotor dynamics measurement data electronically recorded.

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

- Participants must be able to consent to participate themselves
- Be healthy male or non-pregnant female
- Be 21 to 59 years of age
- Must be able to attend in-person sessions at the Mayo Aerospace Medicine and Vestibular Research Laboratory in Scottsdale, AZ.
- Have not used opioids during the preceding 30 days
- Prior use of opioids for pain management

Note: No racial/ethnic groups will be excluded, although all participants must be fluent speakers of English.

Minorities and women are included in subject selection, as long as they meet all eligibility criteria. Vulnerable populations are included to ensure that any benefits from future research will be readily available to these populations. To reduce risk, we will confirm that females are non-nursing and non-pregnant, and women must agree to use an effective method of contraception during the study.

4.2 Exclusion Criteria

- Women who are pregnant or breastfeeding.
- Women who are not practicing an effective form of contraception (condoms, IUD, birth control pill, diaphragm),
- Past or current history of drug or substance use.
- Significant ocular disorder.
- Positive drug test for marijuana, opioids, methamphetamines, cocaine, PCP or other controlled substances.
- History of use of psychoactive drugs within the past 30 days.
- Subjects with a history of cardiopulmonary disease including but not limited to congestive heart failure, obstructive sleep apnea, restrictive lung disease, COPD, moderate to severe asthma and oxygen dependency.
- Subjects currently taking sedatives (including benzodiazepines), muscle relaxants or disassociatives.

4.3 Subject Recruitment, Enrollment and Screening

Screening interviews:

1) Initial telephone interviews will be carried out by Mayo personnel trained to conduct study intake interviews by the AMVRL principal investigator(s).
2) Potential participants will be asked about their health, including their current and past drug use.
3) The Opioid Risk Assessment Tool will be used during screening.

During the intake screening process, participants will be advised that they are being evaluated for participation in studies investigating the effects of various doses of opioids. Participants will also be screened on the state Prescription Drug Monitoring Program database.

Participants who meet the eligibility for specific studies will be contacted and informed that they are eligible for the study using the contact information they provide. General study procedures will be explained.

Eligibility Methodology:

The following eligibility elements for study participation:

1) Successful outcome of the initial telephonic interview and low-risk score (0-3) in the self-reported Opioid Risk tool to be followed by,
2) Lab tests (pregnancy and urine drug testing) for each visit.

Subjects are required to have a negative urine drug and pregnancy test during each session. During each testing session women will be required to have a negative urine pregnancy test. If a woman has a positive urine pregnancy test she will be discontinued from the study. During each testing session, participants are required to have a negative urine drug test. If a subject is found to have a positive drug test, the participant will be discontinued from the study.

Study Design and Methods:

Consent forms include typical notifications of the sponsor and purpose of the study, identification of any risks in the protocol, discussion of privacy dimensions of the study and description of the amount and compensation structure schedule. We brief participants of their right to opt out of the study at any time and for any reason. We include consent forms in the attached draft IRB that are patterned after similar forms used in other persistent sensor wear studies the Mayo team has conducted.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Reasons for early discontinuation:

- Subject safety issues
- Failure of subject to adhere to protocol requirements
- Failed drug test
- Positive Pregnancy test
- Subject seeks treatment for drug-use disorders
- Subject withdraws self for personal reasons
- Subject is considered unstable to receive the second dose of 5mg oxycodone. This will be determined if there is evidence of confusion, vomiting, the respiratory rate falls below 12, oxygen saturation less than 90% on room air.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

There is no follow-up for Withdrawn Subjects in this study, unless the subject has withdrawn for subject safety issues.

5 Study Drug

5.1 Description

Oxycodone (Immediate Release)

Oxycodone is an orally available semi-synthetic opioid analgesic with pharmacologic properties similar to morphine that is indicated for use in the management of acute or chronic moderate to severe pain. Oxycodone is a selective mu receptor agonist that is thought to provide analgesia through interaction with these receptors in both the brain and spinal cord. Like other opioid analgesics in the same class, analgesia occurs without loss of consciousness at therapeutic doses. Other pharmacologic effects include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis and cough suppression.

5.2 Treatment Regimen

This study does not include a treatment regimen. This is a two-way repeated-measure study that consists of two independent variables: "Type of drug (Placebo vs. Oxycodone)" and "Amount of drug (Low Dose vs High Dose).

Oxycodone (Immediate Release) 5 mg over encapsulated in #2 white capsules will be the active medication. The placebo will be provided in #2 white capsules to match the over encapsulated oxycodone immediate release capsules. The active drug or the placebo will be administered orally. Though there are three required visits, no drug or placebo will be administered during the first study visit. During the first visit (A) and after completion of the intake process, the subject's oculomotor dynamics are analyzed and evaluated using the eye tracker devices (EyeLink and EyeTech) with a predetermined, standardized set of oculomotor tasks to establish a baseline for the subject.

For the following two visits the selection of placebo or active drug will be randomized.

The active drug or placebo will be administered orally and each subject will be asked to drink at least 8 ounces of water when swallowing the drug.

During visits B (placebo) & C (Oxycodone), prior to administration of the placebo or drug the subject's oculomotor dynamics are analyzed and evaluated using the eye tracking devices and a predetermined standardized set of oculomotor tasks to establish a baseline for that visit.

As identified in the activity list below, 30 minutes after receiving the placebo or active drug, the same standardized set of oculomotor tasks are administered.

This is a two-way repeated-measure study that consists of two independent variables: "Type of drug (Placebo vs. Oxycodone)" and "Amount of drug (Low Dose vs High Dose).

Dosage - for each of the defined dosages, oculomotor testing will be performed as outlined.

5.3 *Preparation and Administration of Study Drug*

Oxycodone 5 mg immediate release or placebo capsules will be dispensed to investigators by the IDS Pharmacy,5881 E. Mayo Boulevard, Phoenix, AZ 85054. Inquiries regarding study medication can be directed to [redacted], PharmD., IDS Pharmacy Team Lead

([redacted]). Capsules will be administered to subjects to take orally with at least 8 ounces of water.

5.4 Packaging

To maintain the blind, oxycodone immediate release tablets will be over encapsulated into #2 white gelatin capsules. Matching placebo will be #2 white gelatin capsules containing lactose. Over encapsulation and compounding of matching placebo will be performed by IDS Pharmacy staff located at 13400 E. Shea Blvd, Scottsdale AZ, 85259. Total amounts compounded will be dependent on study enrollment. After compounding, completed capsules will be stored in amber bottles at controlled room temperature (15-30 C). At study visits B and C, two capsules will be dispensed to study team for administration to subjects.

Receiving, Storage, Dispensing and Return

5.4.1 Receipt of Drug Supplies

Oxycodone 5 mg immediate release tablets are commercially available and will be obtained from contracted vendor. Number 2 capsules and lactose filler for matching placebo are commercially available and will also be obtained through contracted vendor(s). Full accountability records, receipt, dispense, and destruction of oxycodone 5 mg or placebo capsules used in this investigation will be maintained by the IDS pharmacy. Any discrepancy in inventory will be reported to the study team upon discovery.

5.4.2 Storage

Oxycodone 5 mg immediate release or placebo capsules will be stored in amber bottles at controlled room temperature (15-30C). Capsules will be stored within a secure dispensing cabinet located inside the pharmacy located at 13400 E Shea Blvd, Scottsdale Arizona. Access to the pharmacy location and secure dispensing cabinet is limited to authorized pharmacy personnel only.

5.4.3 Dispensing of Study Drug

Subjects will be randomized in a 1:1 ratio by study staff and treatment assignment will be conveyed to IDS pharmacy staff. Pursuant to an order generated by study physician, IDS Pharmacy staff dispenses two capsules of assigned medication to study team. After dispense IDS Pharmacy staff documents dispense within designated IDS Pharmacy accountability software. Study staff proceeds to document patient administration within the electronic medical record of the subject. Any study medication(s) not utilized will be returned to the pharmacy for documentation and destruction.

Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of Oxycodone 5 mg or placebo capsules compounded and dispensed during the course of the study. Any remaining study medications will be destroyed and destruction will be documented at the conclusion of this study. All accountability records for the study will be maintained indefinitely in the designated IDs accountability software.

6 Study Procedures

This is a two-way repeated-measure study that consists of two independent variables: "Type of drug (Placebo vs. Oxycodone)" and "Amount of drug (Low Dose vs High Dose).

The table below illustrates the study procedure on a per-visit/session basis. In all cases the subject begins with visit A. The order of visits B and C are randomized in order to blind subjects to placebo vs. Oxycodone administration.

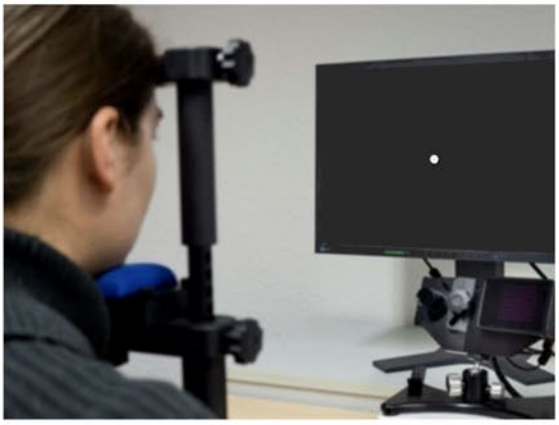
		Visit (A, then randomly B, C)			Time (minutes)
	Assessment	**A**	**B**	**C**	
1	Interview & Consent	X	n/a	n/a	10
2	Physical Examination	X	n/a	n/a	30
3	Urine drug & pregnancy screen, results analysis	X	X	X	60
4	Baseline oculomotor data session, Continuous measurement/observation of heart rate, SpO2 and RR	X	X	X	40
5	First dose (Placebo or Oxycodone) + waiting time, Continuous measurement/observation of heart rate, SpO2 and RR.	n/a	X	X	25
6	2nd oculomotor data session, Continuous measurement/observation of heart rate, SpO2 and RR.	X	X	X	40
7	Second dose (Placebo or Oxycodone) + waiting time, Continuous measurement/observation of heart rate, SpO2 and RR.	n/a	X	X	25
8	3rd oculomotor data session, Continuous measurement/observation of heart rate, SpO2 and RR.	X	X	X	40
	Total Time (minutes)	**270**	**230**	**230**	

As noted in the above table, from Step 4 (i.e. baseline test before receiving the first dose of oxycodone) till the end of the experiment, the oxygen saturation levels and heart rate will be continuously monitored through a finger pulse oximeter. Respiratory rate will be clinically monitored by the investigators. These physiological measures during the experiment serve for safety monitoring purposes after administering oxycodone.

6.1 Testing System Configuration

A two-station set up will be utilized for the testing in this project. The first station will run the primary visual stimulus testing plan using EyeLink eye-tracking device. And the second station will be configured to run Mayo Clinic's proprietary Oculo-Cognitive Addition test (OCAT) using EyeTech eye-tracking device.

Primary Station



The primary station consists of a standard computer and color LCD screen with a 15" diagonal, 16:9 format and an SR Research Eyelink eye tracking system. A standard head rest device provided by SR Research will be mounted in front of the screen to help minimize error induced by inadvertent head movement of the subject during the testing protocol. This device provides support while allowing the subject to maintain free movement at all times.

The computer screen is placed approximately 50cm from the subject's eyes such that the display stimuli achieve the desired visual angle within the subject's field of view.

OCAT Station

The subjects will do Oculo-Cognitive Addition Test (OCAT) in which they will have to look for numbers on a screen and add these numbers together. OCAT will be presented on a 17" laptop screen with attached eye tracking device at the bottom part. The detailed OCAT description is attached in the supporting documents.

6.2 Visual Tasks

A suite of visual tasks will be presented to the subjects during each visit. In all but the Free Viewing task (details below), the visual stimulus presented will be a fixation spot, which is a "donut" shape approximately 0.2 degrees in radius. This small donut shape will be white on a black or dark grey background.

Fixation: Test of visual fixation to measure microsaccades, spontaneous nystagmus, and gaze-evoked nystagmus. The stimulus presented on the monitor screen. The subject is instructed to look at the fixation spot as accurately as possible. Thirty-second trials are conducted with the fixation spot starting at the center and then may be positioned randomly 20° left/right, 15° up/down and then center again.

Saccade speed: Test of saccade velocity and intersaccadic intervals. The stimulus consists of two fixation spots 20/15 degrees apart horizontally/vertically. The subject is instructed to look back and forth between the two spots as fast as possible for 50 seconds. The trials are random, first horizontal or vertical. The subjects starts on fixation at the center and is then instructed to look first at the target on the left/up then start jumping.

Saccade accuracy: Test of saccade accuracy. The stimulus consists of one fixation spot. The subject is instructed to look at the target as soon as it moves, as accurately as possible. Each trial includes 1 second fixating at the center, then the target moves for 1 second, and finally it moves back again to center. For horizontal movement, the target first moves to 5°, then -5°, then 10°, then -10°, repeating at 5° increments until -20°, then decreasing by 5° increments to 5° again. The same is true for vertical movement but only up to 15°. Then the whole sequence of horizontal and vertical movements is repeated.

Visually guided: Test for cognitive control over saccades. The stimulus consists of one fixation spot. The subject fixates on a central fixation point. Then, the central fixation point is switched off, and a visual cue is presented in a pseudorandom position at 20° eccentricity, right or left of the central fixation point. Subjects are instructed to move their eyes directly and as accurately as possible to the cue as soon as it appears. After 1000 ms, the cue is switched off and the central fixation point is re-illuminated. After an inter-trial interval of 2500–3500 ms, the next trial begins.

Antisaccade: Test for cognitive control over saccades. The stimulus consists of one fixation spot. The subject fixates on a central fixation point. Then the central fixation point is switched off and after 200 ms ('gap'), a visual cue is presented at 20° eccentricity right or left of the central fixation point. Subjects are instructed to move their eyes in the direction opposite to the cue as soon as it appears. Subjects are given no instructions for saccade accuracy. After 1000 ms, the cue is switched off and the central fixation point is re-illuminated. After an inter-trial interval of 2500–3500 ms, the next trial begins.

Memory-guided: Test for cognitive control over saccades. The stimulus consists of one fixation spot. The subject fixates on a central fixation point. Then, a visual cue is presented for 100 ms in one of 10°, 12.5°, 15°, 17.5°, 20°, while subjects continued fixating. After a delay of 5000 ms, the central fixation point is switched off and subjects move their eyes directly and as accurately as possible to the remembered cue position. After 3000 ms, the central fixation point is re-illuminated and after an inter-trial interval of 5000 ms the next trial begins.

Pursuit: Testing of cerebellar control of smooth pursuit. The stimulus Target moves horizontally and vertically with a sinusoidal acceleration amplitude of 7.5 deg and frequency increasing from 0.5 Hz to 3 Hz during 60 sec every 10 seconds. (6 speeds). Repeat 2 times.

Free Viewing: Testing of cognitive control of visual scanning. The stimulus presented is a set of 20 photographs, each presented for 15 seconds. The subject is instructed to freely view the image in any way they wish. The entire catalog of images is attached in the supporting documents.

OCAT Methodology:
OCAT consists of completing as rapidly as possible 12 trials of summing three consecutive numbers shown separately on three consecutive blank screens. The position of the number on each screen is random and hence requires visual scanning along with the cognitive processing of adding three numbers. The step by step procedure to proceed through each trial is as follows:
1. The first blank screen displays a single digit number with the green background at a random position.
2. The subject verbally calls out the number and then hits the space-bar key to go to the second screen.
3. The second blank screen displays the next single digit number with the green background at a different random location and the previous number disappears.
4. The subject has to sum the current number with the previous number to verbally call-out the sum of two numbers and then proceed to the third screen by hitting again the space-bar key.
5. The third screen displays the next (third) single digit number with the red background at a different random location and the previous number disappears.
6. The subject has to sum the current number with the sum of the last two numbers to verbally call-out the total sum of all the three numbers.
7. The red background of the third number indicates the "end of the trial".
8. On hitting the space-bar key, the subject proceeds to the first screen of the next trial and repeats the same procedure for the next trial.

Every trial will have different set of three numbers at different locations.

Statistical Plan

6.3 Sample Size Determination

Based on our previous study on testing OCAT for cognitive performance during hypoxic incapacitation (IRB # 16-007938), it showed that an average OCAT completion time of 63 seconds, with a standard deviation of 15 seconds, and a sample size of 25 subjects would provide 90% power, if it showed at least 19 seconds (i.e., 30%) of incremental change in the OCAT completion time.

6.4 Methods

Data Collection

Data collection is performed by eye tracking systems coupled with a PC which presents the test stimulus to the participant. As the stimuli are presented, the eye tracking systems record the minute characteristics of the subject's eye movement in a tabular format consisting of rows and columns. Each row represents the eyes' state, (gaze coordinates, pupil size) for an individual sampling period. This data is recorded to disk and the filename encoded such that it may be referenced against the subject's visit mission (e.g. baseline, placebo, and drug). The data recorded in this file is completely anonymized and cannot be tied back to the individual.

Descriptive Statistics

Univariate descriptive statistics and frequency distributions will be calculated, as appropriate for eye tracking features related to fixations (average fixation time-length, average fixation size, fixation count, total fixating time, and fluctuation in fixation time length), saccades (average saccadic length, total saccadic time, saccade count, saccadic amplitude, and saccadic velocity), and blinks (blink rate, blink duration, and inter-blink duration) across baseline, placebo and drug.

Handling of Missing Data

In cases where sample data is missing or corrupted the entirety of the data relative to the single test with the missing data will be flagged and excluded from the analysis.

Primary Hypothesis:

This study aims to verify that temporary neurologic impairment by Oxycodone has a measurable effect on the oculomotor system and that this effect is clearly differentiated from the oculomotor dynamics of non-impaired individuals.

Interim Analysis

Incoming data will be analyzed periodically over the course of this project in an effort to monitor the progress and early-stage outcomes. Data files will be initially inspected to ensure there is no corruption of the data and that the data stored is in the expected format. Data will also be processed periodically and an analysis performed to determine if the early findings support the hypothesis.

6.5 Subject Population(s) for Analysis

All-completed population: Only subjects who completed ALL study related procedures and follow-up will be included

7 Safety and Adverse Events

7.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event
An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event
Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity
- birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as *24 hours* (i.e. 4 half-lives, which is when drug is expected to be eliminated from the body [assuming t1/2 of 6h (3.5 - 5.5)]) following the last administration of study treatment.

Pre-existing Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

7.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting

Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

7.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

7.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

Information collected on the adverse event worksheet (*and entered in the research database)*:

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention*):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5**)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

*** Relationship Index Example**
The relationship of an AE to the Investigational Drug is a clinical decision by the sponsor-investigator (PI) based on all available information at the time of the completion of the CRF and is graded as follows:

1. Not related: a reaction for which sufficient information exists to indicate that the etiology is unrelated to the study drug; the subject did not receive the study medication or the temporal sequence of the AE onset relative to administration of the study medication is not reasonable or the event is clearly related to other factors such as the subject' s clinical state, therapeutic intervention or concomitant therapy.

2. Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations.

3. Possible: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but which could also be explained by concurrent disease or other drugs or chemicals; information on drug withdrawals may be lacking are unclear.

4. Probable: a clinical event including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (de-challenge): re-challenge information is not required to fulfi1 this definition.

5. Definite: a reaction that follows a reasonable temporal sequence from administration of the drug, or in which the drug level has been established in body fluids or tissues, that follows a known or expected response pattern to the suspected drug, and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure (re-challenge).

7.4 Stopping Rules

1. Reasons for early discontinuation will be related primarily to safety issues.

2. Volunteers will not be allowed to enter the study if they are seeking treatment and/or meet criteria for moderate to severe Drug Use Disorders.

3. If a woman is found to be pregnant or nursing she will be discontinued from the study.

4. If the subject is considered unstable to receive the second dose of 5mg oxycodone. This will be determined if there is evidence of confusion, vomiting, the respiratory rate falls below 12, oxygen saturation less than 90% on room air.

7.5 Medical Monitoring

The oxygen saturation levels and heart rate will be continuously monitored through a finger pulse oximeter throughout the experiment. And the respiratory rate will be clinically monitored by the investigators by observing the breathing of the subject.

The investigators will clinically monitor the subject during the study and if there is any indication of untoward alteration of vital signs (abnormal oxygen saturation, heart rate or respiratory rate), then the emergency response team at the clinic campus will be activated by calling the operator.

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

7.5.1 Internal Data and Safety Monitoring Board

The research team will monitor participant safety continuously, with frequent reporting to the study principal investigator. The principal investigator will report any adverse events or unanticipated problems involving risks to research participants or others to the IRB.

8 Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

8.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

8.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be

printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Management

Data captured by the eye tracking system is written first to the local hard disk of the computer running the tests. This data is then automatically backed-up to the dedicated data management system.

Data Processing

This two-way repeated-measure study consists of two independent variables: "Type of drug (Placebo vs. Oxycodone)" and "Amount of drug (Low Dose vs High Dose).

The analysis of eye movements will be focused on four separate categories: blinks, pupillary dynamics, fixations and saccades. We plan to use raw scan-paths to extract features related to fixations and saccades. The features related to fixations are average fixation time-length, average fixation size, fixation count, total fixating time, and fluctuation in fixation time length. The features related to saccades are average saccadic length, total saccadic time, saccade count, saccadic amplitude, and saccadic velocity. The features related to blinks will be blink rate, blink duration, and inter-blink duration. In addition, the features related to pupillary dynamics will be pupil diameter, and fluctuation in pupil size. Two-way Repeated measures ANOVA (rmANOVA) on the eye-tracking features will be implemented to assess the effect of drug (Oxycodone vs. Placebo), amount (high dose vs. low dose) and also the interaction between drugs and amount.

Data Security and Confidentiality

The data that will be collected will reside on secure servers and protected computers. Data will be de-identified immediately after capture. The study documentation will be stored in locked cabinets in the investigators secure office

Data Quality Assurance

Eye movement data is recorded to disk and the filename encoded such that it may be referenced against the subject's visit mission (e.g. baseline, placebo, impaired). The data recorded in this file is completely anonymized and cannot be tied back to the individual.

Data Clarification Process

8.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for;

1. Record of consent and screening results will be retained at least 3 years from the date of consent, after which materials containing IHI will be shredded or burned. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy"[redacted]

Whichever is longer.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

10 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed

by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

11 Study Finances

11.1 Funding Source

This study will be funded by Zxerex Corporation.

11.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

11.3 Subject Stipends or Payments

Study participants will be offered $450.00 to reimburse them for the time spent in the study and $100.00 for all travel expenses after completing the entire study.

12 Publication Plan

This is the first of a series of studies. It is not anticipated that there will be academic publication opportunities arising from the work conducted under this project.

13 References

- "Opioid Basics - Understanding the Epidemic (current version)" - *Center for Disease Control and Prevention* - https://www.cdc.gov/drugoverdose/epidemic/index.html
- "Oxycodone HCl (current)" - *Prescribers' Digital Reference* - https://www.pdr.net/drug-summary/Oxycodone-Hydrochloride-Tablets-oxycodone-hydrochloride-3271.3140
- "Unsupervised Clustering Method To Detect Microsaccades" - *Journal of Vision* - Jorge Otero-Millan-Jose Castro-Stephen Macknik-Susana Martinez-Conde, February, 2014
- "Saccades during Attempted Fixation in Parkinsonian Disorders and Recessive Ataxia: From Microsaccades to Square-Wave Jerks" - *PLOS One* - Jorge Otero-Millan, Rosalyn Schneider, R. John Leigh, Stephen L. Macknik, Susana Martinez-Conde, March, 2013

- "Simultaneous Recordings of Human Microsaccades and Drifts with a Contemporary Video Eye Tracker and the Search Coil Technique" - *PLOS One* - Michael B. McCamy, Jorge Otero-Millan, R. John Leigh, Susan A. King, Rosalyn M. Schneider, Stephen L. Macknik, Susana Martinez-Conde, January 2015

- "Distinctive Features of Saccadic Intrusions and Microsaccades in Progressive Supranuclear Palsy" - *The Journal of Neuroscience* - Jorge Otero-Millan, Alessandro Serra, R. John Leigh, Xoana G. Troncoso, Stephen L. Macknik, Susana Martinez-Conde, March, 2011

- "Saccadic Eye Movement Metrics Reflect Surgical Residents' Fatigue" - *Annals of Surgery* - Leandro L. Di Stasi, PhD, Michael B. McCamy, PhD, Stephen L. Macknik, PhD, James A. Mankin, MD, Nicole Hooft, MD, Andres Catena, PhD, and Susana Martinez-Conde, PhD, April 2014

- "Spatial statistics and attentional dynamics in scene viewing" - *Journal of Vision* - Ralf Engbert, Hans A. Trukenbrod, Simon Barthelmé, Felix A. Wichmann, January 2015 - https://jov.arvojournals.org/article.aspx?articleid=2213249

14 Attachments

Attached documents include:

- OCAT description
- Eyelink eye-tracker specifications documentation
- Images for Free Viewing test