Study Project: Non-intrusive detection of temporary neurologic impairment by opioids
Award #: 1R43DA049684-01

NCT #: Pending
Date: 07.28.2022

Document Type: Study Protocol & Statistical Analysis Plan (SAP)

Study Protocol & Procedures

The objective of this study is to ascertain the influence of impairment by oxycodone on the oculomotor system as measured by an infrared videographic eye tracking system. Specifically:

- Measurement of opioid-induced changes in oculomotor activity, with respect to undosed (control) and placebo conditions
- Comparison of opioid-induced oculomotor effects from low- and high-dose treatments, to describe a dose-response effect, if present

Subjects are tested for oculomotor effects of ingested oxycodone, using an SR EyeLink 1000 eye tracking device consisting of an infrared camera, console and control equipment to sample orientation and pupil size at 500 frames per second. Binocular orientation, eye movement, and pupil area were collected, with the eye movements characterized as involuntary *microsaccades* (occurring during fixational events) or intentional *saccades* (movement between fixational events). Subjects were subjected to several randomly ordered visual tests, including visual fixation, saccade speed and accuracy, cognitive control over saccades, cognitive control over visual scanning, pursuit and activity during free viewing of randomly presented images. These tests required subjects to watch or follow a stimulus consisting of a small annulus over a gray background. An additional test measured pupillary reactivity to sudden changes in screen illumination.

Tests were conducted over three different sessions, each consisting of three 40-min timeblocks, separated by 30-min rest periods. Each timeblock contained two cycles of each eye-tracking test, and one sequence testing pupil reactivity. Data were collected in the *control*, *placebo*, *low-dose* oxycodone (5 mg) and *high-dose* oxycodone (10 mg) conditions.

STATISTICAL PROCEDURES

Eye tracking time series are processed with blink detection and feature extraction procedures. Saccadic and microsaccadic movements were then detected using a modified Engbert algorithm (R Engbert, R Kliegel, *Psychol. Sci.* 15(6), 2004). Test-specific features (whose full descriptions are withheld as trade secrets) of microsaccade data were analyzed using 2-way linear ANOVA models: the effect of Condition is evaluated against the effect of Trial (1-6) to identify significant dose-dependent changes. Features of saccade data (combined across trials to achieve satisfactory sample size) were compared between Condition levels using a 1-way ANOVA. Features that exhibited effects of Condition in the first analysis were tested with *post hoc* t-tests to evaluate the presence of dose-dependent effects. The effect of acute eye fatigue is also investigated with another 2-way ANOVA of Condition and Trial effects: in this case, the Trial comparisons were the first trial in each timeblock (Trials 1, 3, 5) versus the second trial in each timeblock (Trials 2, 4, 6).

After the opioid effects on oculomotor behavior are established, a binary classifier will be constructed to accurately predict opioid impairment. High-dose and low-dose opioid conditions were combined into an *opioid* condition, which will be evaluated against the combined *placebo* and *control* conditions, for all test types.