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The Relationship between Pupil Diameter and Other Measures of Opioid Withdrawal During Naloxone Precipitated Withdrawal

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Abstract

Background: Understanding mechanisms of physiological opioid withdrawal symptoms can inform treatment strategies. This secondary analysis evaluated the association between mydriasis (dilated pupils), a commonly-assessed opioid withdrawal metric, with self-and observer-rated opioid withdrawal severity.

Method: Ninety-five participants with opioid physical dependence were stabilized with morphine before receiving an injection of the opioid antagonist naloxone to precipitate withdrawal. Pupil diameter, the Subjective Opiate Withdrawal Scale (SOWS), and the Clinical Opiate Withdrawal Scale (COWS) were collected at baseline and in 15-minute intervals for 120 minutes following naloxone administration. Pearson product-moment correlations and linear regressions characterized the relationships between pupil measurements (baseline and peak naloxone-induced) and self-and observer-rated measures of withdrawal. Repeated-measures ANOVAs tested whether self and observer-rated withdrawal severity corresponded to unique patterns in pupil changes.

Results: Baseline pupil diameter significantly correlated with SOWS and COWS peak scores. Peak naloxone-induced pupil diameter significantly correlated with SOWS scores only. Peak changes in pupil from baseline did not correspond to peak changes in self-and observer-rated withdrawal scales.

Conclusions: This study suggests that pupil diameter measurements were more closely associated with acute opioid withdrawal severity than changes in pupil diameter. Prospective research examining the mechanisms underlying the relationship between pupil diameter and opioid withdrawal severity are warranted.

Keywords

Opioid Use Disorder; Opioid Withdrawal; Pupil; Naloxone; Morphine

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1. Introduction

The prevalence of opioid use disorder (OUD) is a public health crisis (Birnbaum et al., 2011; Han et al., 2018), and increased rates of opioid use-related morbidity and mortality have corresponded with rising economic and societal burden in the U.S. (Reinhart et al., 2018). Managing opioid withdrawal is critical for the successful treatment of OUD (Gowing et al., 2009; Northrup et al., 2015; Whitley et al., 2010). Using valid and objective measures of opioid withdrawal could enhance clinical practice.

Pupil diameter can be used as an objective measure of opioid effects. Pupil diameter reliably constricts (miosis) in response to opioid agonists, and several reports indicate that the magnitude of this change is associated with an individual's history of opioid use (Ghodse et al., 1995; Higgins et al., 1985; Kollars and Larson, 2005; Robinson et al., 1974; Tress et al., 1978, 1979). As a result, pupil diameter has become a commonly-used metric for assessing opioid agonist effects in humans. Given the complementary nature of opioid agonist and antagonist effects, mydriasis (pupil dilation) is often measured as an objective marker of opioid withdrawal severity, with larger pupils corresponding to increased severity of opioid withdrawal (Rosse et al., 1998; Tompkins et al., 2009). Despite being considered a metric of opioid withdrawal for decades, the exact relationship between pupil diameter and withdrawal severity has not been well-characterized.

As part of a larger clinical trial, we recently completed a laboratory evaluation of opioid withdrawal precipitated with the opioid antagonist naloxone in persons physically-dependent on opioids (Dunn et al., 2017). Pupil diameter and opioid withdrawal symptoms were measured while participants were treated with the opioid agonist morphine (baseline) and at subsequent time points following naloxone administration. These data were analyzed to examine the relationships between baseline pupil diameter, naloxone-induced pupil diameter, and self-reports and observer-ratings of opioid withdrawal. We hypothesized that both baseline and peak naloxone-induced pupil diameter measurements would be positively correlated with clinical and self-reported opioid withdrawal assessments.

2. Methods

Details relevant to the present analyses are described here and the complete methods for the parent study can be found elsewhere (Dunn et al., 2017; Clinicaltrials.gov identifier: NCT01188421). Relevant to the present analyses, participants completed a naloxone challenge to assess opioid physical dependence levels as part of the parent study.

2.1. Participants

Eligible participants (1) were aged 18–60, (2) met DSM-IV criteria for opioid dependence, and (3) provided a urine sample that tested positive for recent opioid use or exhibited opioid withdrawal by the end of the screening session. Participants were excluded if they (1) were pregnant, (2) were currently enrolled in opioid agonist treatment, (3) had significant medical and/or psychiatric illnesses, (4) had physical dependence on benzodiazepines or alcohol that required medical intervention, (5) had hypotension, (6) had a history of seizures, or (7) had a known allergy to study medications. Only participants with a complete set of pupil

measurements at all time points were included in the current analyses (*N*=95 of 103 originally enrolled).

2.2. Study Measures

2.2.1. Subjective Opiate Withdrawal Scale (SOWS)—The SOWS is a valid and reliable self-report assessment comprised of 16 opioid withdrawal symptoms (Handelsman et al., 1987). Participants rate the severity of each symptom on a scale of 0 (not at all) to 4 (extremely). Symptoms evaluated with the SOWS include: Anxiety, Cold Flashes, Yawning, Goose Flesh, Shaking, Restless, Nauseous, Vomiting, Stomach Cramps, Bone/Muscle Aches, Feel Like Using, Perspiring, Eyes Tearing, Nose Running, Hot Flashes and Muscle Twitching. Values are summed for a total score (0–64), to characterize overall severity of withdrawal.

2.2.2. Clinical Opiate Withdrawal Scale (COWS)—The COWS is a valid assessment tool for acute opioid withdrawal, and is comprised of 11 items that are scored by an observer on symptom-specific categorical scales with unique ranges (Tompkins et al., 2009; Wesson and Ling, 2003). Within each naloxone challenge session, the same COWS rater completed all assessments. Raters completed a structured training program to ensure accurate and reliable COWS scoring. For the analyses in this report, COWS total score values were computed in two ways, including or removing a pupil-specific question (referred to as COWS-Modified [COWS-M]; revised range 0–43). This modification was to ensure that any COWS-specific results were not driven by the inclusion of a pupil-specific item. Results did not differ depending on the version of COWS used so only COWS-M results are reported in this report. Symptoms evaluated with the COWS-M include: Runny Nose/Tearing, Anxiety, Goose Flesh, Yawning, Tremors, Restless, Sweating, Bone/Muscle Aches, Gastrointestinal Problems and Resting Pulse Rate.

2.2.3. Pupil Diameter—Pupil diameter measurements in millimeters were obtained using a digital pupilometer (Neuroptics, Inc.) under consistent lighting and environment conditions. The primary outcome for pupil size was pupil diameter in millimeters.

2.3. Study Procedures

Eligibility was assessed at a screening visit where participants completed demographic and drug use history questionnaires and provided urine samples. All study procedures took place in a controlled, residential setting. Upon study admission, participants were stabilized on 30 mg of morphine delivered subcutaneously (SC) four times daily by medical staff. The naloxone challenge occurred after participants had been stabilized on morphine for 4–7 days.

On the day of the challenge session participants received a dose of morphine at 07:00. Fifteen minutes prior to naloxone administration (10:45), participants provided baseline withdrawal ratings and researchers collected pupil measurements. At 11:00, participants received a 0.4 mg intramuscular dose of naloxone. SOWS and COWS ratings and pupil measurements were then collected every 15 minutes for a total of 120 minutes, resulting in one pre-naloxone (i.e., baseline) and eight post-naloxone measurements.

2.4. Statistical Method

This study hypothesized that baseline and peak naloxone-induced pupil diameter would be significantly associated with self-and observer-rated opioid withdrawal severity. Naloxone-induced outcomes were characterized with the peak naloxone-induced pupil diameter, SOWS and COWS-M total scores, representing the most severe expression of withdrawal. Matched-pairs t-tests and Cohen's *d* effect sizes were computed to characterize changes from baseline to peak naloxone-induced pupil diameter, SOWS and COWS-M. Changes in pupil diameter across time points were tested using a one-way repeated measures ANOVA (RM-ANOVA) with Bonferroni post-hoc analyses comparing time points.

Pearson correlation coefficients characterized the relationship between pupil diameter (baseline and peak naloxone-induced) and peak naloxone-induced self-and objective-rated withdrawal measures (SOWS and COWS-M total scores). Next, to characterize the relationship between these variables while controlling for baseline scores, Pearson correlation coefficients assessed the relationship between peak *change from baseline* pupil diameter and peak *change from baseline* SOWS and COWS-M total scores (peak naloxone-induced score – baseline score). As a sensitivity analysis, pupil diameter was also examined as a percent change from baseline and correlated with percent change from baseline SOWS and COWS-M scores; results from these analyses replicated the pattern observed in other analyses, and the results of this study utilized baseline pupil diameter, peak pupil diameter, and change-from-baseline peak pupil diameter in millimeters (as opposed to percent change) because they were deemed to have greater face validity and potential for generalizability.

Finally, SOWS and COWS-M scores were categorized into quartiles based upon peak naloxone-induced scores in order to analyze withdrawal severity measures as a categorical variable. Pupil diameter across time points (within subjects factor; baseline and 15, 30, 45, 60, 75, 90, 105 and 120 minutes naloxone-induced) were compared across the four withdrawal quartiles (between subjects factor) using a RM-ANOVA. Bonferroni post-hoc analyses examined differences between quartile groups when a main effect of Quartile was observed. All analyses were conducted using SPSS version 25 and alpha levels were set at $p<.05$.

3. Results

3.1. Participant Characteristics

Demographic, socioeconomic and drug-use history characteristics of the final sample (N= 95) are summarized in Table 1.

3.2. Baseline and Peak Naloxone-induced Values

Pupil increased a mean 1.4 mm (SD = 0.9) from baseline (M = 4.4, SD = 1.3) to the peak naloxone-induced assessment (M = 5.8, SD = 1.3; Table 1), $t(94) = -15.7$, $p < .01$, $d = 1.6$. The majority of peak naloxone-induced pupil diameter occurred at the 15-(49.5%) and 30-minute (36.3%) time points. All post-naloxone pupil measurements were significantly different from baseline pupil measurements (p's < .05; Figure 1)

SOWS total scores increased a mean of 23.2 points (SD = 13.9) from baseline (M = 2.7, SD = 3.5) to the peak naloxone-induced assessment (M = 25.9, SD = 14.0), $t(94) = -16.3$, $p < .01$, d = 1.7. The majority of peak SOWS total scores occurred at the 15-(46.9%) and 30-minute (35.6%) time points.

COWS-M total scores increased a mean of 9.8 points (SD = 5.8) from baseline (M=1.3, SD = 1.3) to peak naloxone-induced assessment (M=11.5, SD = 6.1), $t(94) = -19.0$, $p < .01$, d = 1.7. The majority of peak naloxone-induced measurements occurred at the 15-(49.4%) and 30-minute (31.5%) time points.

3.3. Associations between Pupil and Withdrawal Ratings

Baseline pupil diameter was significantly and positively correlated with peak total SOWS scores (r = 0.33, $p < 0.01$) and peak total COWS-M scores (r = 0.25, $p < 0.05$). Peak naloxone-induced pupil diameter was also positively and significantly correlated with peak total SOWS scores (r = 0.26, $p < 0.05$) but not peak total COWS-M scores (r = 0.14, p = 0.18).

3.4. SOWS and COWS-M Total Scores Peak Change from Baseline

Peak pupil diameter change from baseline was not significantly correlated with total SOWS peak change from baseline, $r = -0.11$, p = 0.30 nor total COWS-M peak change from baseline, $r = -0.16$, p = 0.12.

3.5. Associations between Pupil Diameter and Peak Withdrawal Severity Quartiles

3.5.1. SOWS Total Score—RM-ANOVA with a Greenhouse-Geisser correction determined that pupil diameter differed significantly across time points ($F(5.38, 489.62) = 33.70$, $p < .001$) and between SOWS quartile groups ($F(3, 91) = 5.31$, $p < .01$). Bonferroni-corrected post-hoc tests indicated that pupil diameter across time points was significantly smaller within the first SOWS quartile group (M = 4.34, SE = 0.23) as compared to the second (M = 4.93, SE = 0.26, p=0.04), third (M = 5.41, SE = 0.25, p=0.01), and fourth (M = 5.57, SE = 0.25, p=0.003) SOWS quartile groups.

3.5.2. COWS-M Total Score—RM-ANOVA with a Greenhouse-Geisser correction determined that pupil diameter differed significantly across time points ($F(5.50, 500.76) = 33.24$, $p < .001$). The main effect of COWS-M peak quartile, though, was not significant ($F(3, 91) = 18.18$, p = .31; Figure 1B).

4. Discussion

This study evaluated the relationship between pupil dilation and other opioid withdrawal symptoms during a naloxone challenge among OUD patients who were maintained on morphine in a controlled laboratory setting. Baseline pupil diameter measured prior to naloxone administration was significantly associated with all self-report and clinical measures of withdrawal, while peak pupil diameter following naloxone administration was only significantly associated with self-reported withdrawal. Surprisingly, the magnitude of naloxone-induced pupil diameter change did not correspond to changes in naloxone-induced

self-or observer-rated withdrawal. The only other study, to our knowledge, that investigated this relationship used data from 19 opioid-dependent men who were undergoing spontaneous withdrawal from opioids, and the pattern we observed between pupil diameter and other measures of naloxone-precipitated withdrawal largely replicated what was observed during spontaneous opioid withdrawal (Rosse et al., 1998). As such, our data expand upon previous studies by evaluating this topic in a large sample of men and women, with controlled opioid agonist and antagonist dosing, and using precise measurement of pupil diameter. Altogether these data suggest that regardless of the severity of peak self-reported or observer rated withdrawal, the magnitude at which pupil diameter increased was a fixed increment (Figure 1). We know of no studies that have reported a positive relationship between pupil diameter increases (at the level of millimeter as measured here) and severity increases of either self-reported or observer-ratings of withdrawal.

While changes in pupil diameter following naloxone did not correspond to changes in other measures of opioid withdrawal, baseline and peak naloxone-induced pupil diameter did correspond to measures of opioid withdrawal. Previous studies have indicated that pupil diameter is heavily impacted by genetics and pre-existing levels of physiological tolerance and dependence (Hammond et al., 2000; He et al., 2009; Higgins et al., 1985; Kollars and Larson, 2005; Tress, 1978). Accordingly, we stratified the relationship between pupil diameter and other withdrawal measures on peak SOWS/COWS-M scores but still found no relationship between changes in pupil diameter and other withdrawal measures. Therefore, it is possible that pupil diameter prior to the onset of withdrawal reflects a preexisting difference in physical dependence and genetic differences among individuals with OUD that may be a better predictor of ultimate self-reported and/or observer-rated withdrawal severity than the magnitude of pupil change during the withdrawal period. If true, then determining the baseline pupil diameter threshold that is associated with greater future withdrawal severity could be of clinical utility.

There are some limitations that should be considered when interpreting these findings. First, this study was not prospectively designed to assess the relationship between pupil diameter and opioid withdrawal symptoms, and although collecting pupil diameter and withdrawal measurements every 15 minutes is a granular approach for the purpose of capturing the course of naloxone-induced withdrawal, more frequent measurements of pupil diameter might further enhance our understanding of the relationship between the physiological and subjective human experience of opioid withdrawal. Indeed, two small studies suggest that pupillary change may precede the onset of subjective withdrawal symptoms during opioid detoxification, though this level of sensitivity was not possible to assess in our dataset (Eissenberg et al., 1997; Fudala et al., 1990). Second, it is unclear how well naloxone-precipitated withdrawal approximates the clinical experience of spontaneous withdrawal, although a recent study suggests that a naloxone challenge is associated with withdrawal phenotypes that predict withdrawal severity (Dunn et al., 2018). Future studies should assess the degree to which pupillary change can function as a biological indicator of physiological and self-reported symptoms of opioid withdrawal in clinical settings. Additional studies should determine which individual differences influence baseline pupil diameter so that the measure is more fully understood.

Altogether, these results provide initial evidence that baseline pupil measurement in a controlled experimental setting are associated with naloxone-precipitated opioid self-and observer-ratings of opioid withdrawal severity, and that pupil diameter prior to the onset of withdrawal could be a unique indicator of subsequent withdrawal symptoms in clinical settings. These findings advance the general understanding of pupil as an index of opioid withdrawal severity and support additional research to prospectively evaluate these associations.

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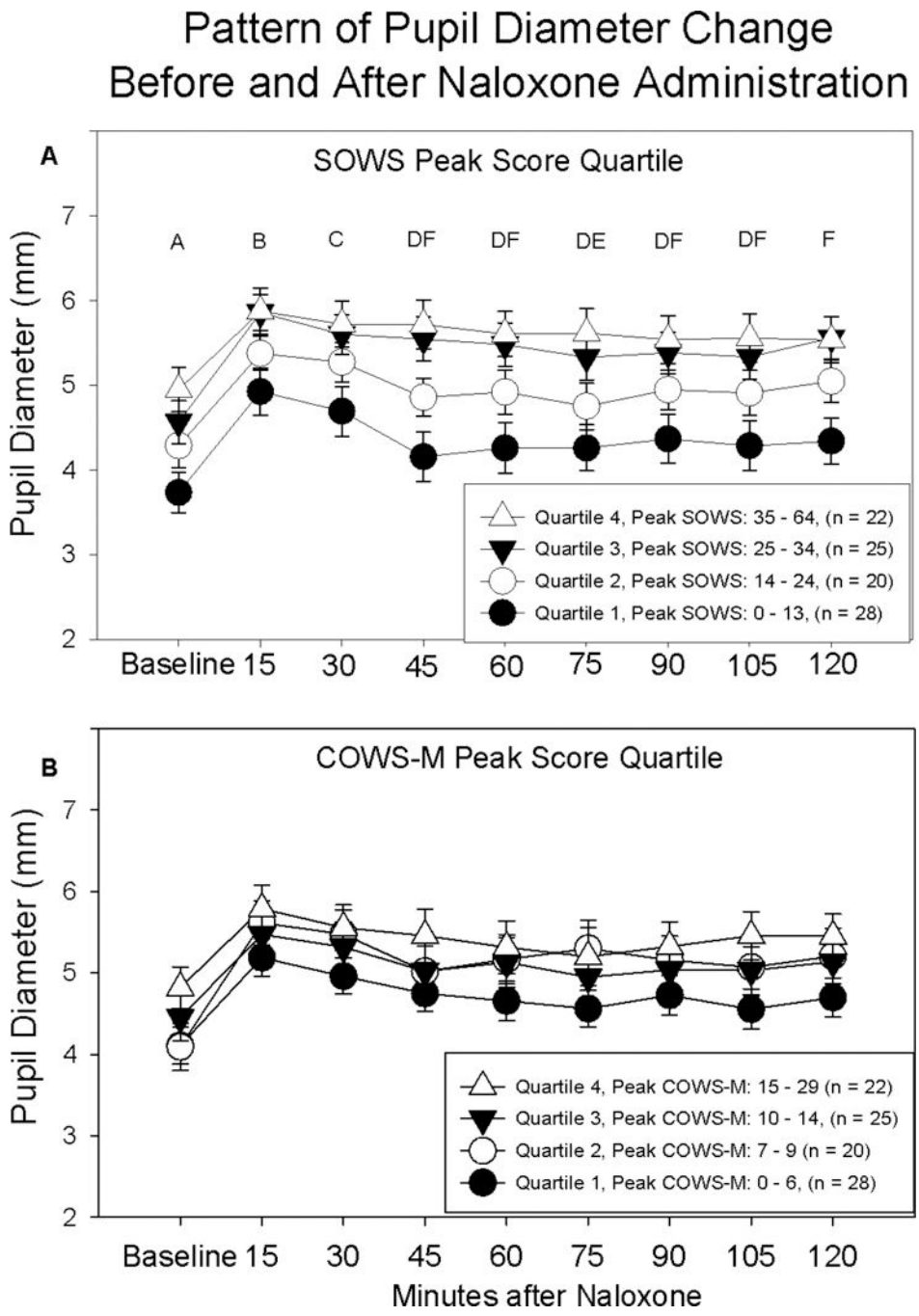

Figure 1. Pattern of Pupil Diameter Change Before and After Naloxone Administration

Pupil diameter in millimeters before and after naloxone administration as a function of peak SOWS and COWS-M total scores divided into quartiles. Quartile 1 represents the lowest withdrawal severity group, and quartile 4 represents the highest withdrawal severity group. Pupil diameter across time differed by SOWS peak score quartile (Panel A) such that the lowest SOWS peak score quartile had significantly smaller pupils across time versus each of the other three quartiles. Main effects of quartile on COWS-M and Quartile X Time Interactions were not significant. Post-hoc tests for the main effect of time on pupil diameter

are illustrated in Panel A. Time points with letters in common are not significantly different from one another, $p < .05$.

Table 1.

Participant Characteristics and Withdrawal Measures

Characteristics *N* = 95	
% Male	87
% African American	54
Age in years	41.2 ± 10.2
Body Mass Index (BMI)	25.9 ± 5.3
Years of Education	12.2 ± 1.6
% Cigarette Smoker	65
Duration of Heroin Use in Lifetime, years	11.6 ± 9.8
Heroin Use Last 30 days	
Number of Days	24.8 ± 8.6
% Participants Used Every Day for Last 30	41
Withdrawal Measures	
SOWS (range: 0–64)	
Baseline	2.7 ± 3.5
Peak during withdrawal period	25.9 ± 14.0
COWS [with pupil item] (range: 0–48)	
Baseline	1.7 ± 1.8
Peak during withdrawal period	13.1 ± 6.1
COWS-M [without pupil item] (range: 0–43)	
Baseline	1.2 ± 1.3
Peak during withdrawal period	11.5 ± 6.1
Pupil Diameter (millimeters)	
Baseline	4.4 ± 1.3
Peak during withdrawal period	5.8 ± 1.3

Note. Statistics are expressed as means ± standard deviations unless otherwise noted. SOWS=Subjective Opiate Withdrawal Scale. COWS=Clinical Opiate Withdrawal Scale, COWS-M= COWS-modified to remove pupil item.