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A Pilot Study of Automated Pupillometry in the Treatment of Opioid Use Disorder

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Introduction/Background: A rough, visual estimate of pupil size is used in grading the severity of opioid withdrawal. Few studies have examined the clinical utility of more precise automated pupillometry measurements.

Methods: This prospective cohort study enrolled 27 patients receiving opioid agonist therapy (OAT) to treat cravings or withdrawal during an acute hospitalization. Six sets of automated pupillometry measurements were obtained at regular intervals before and after administration of OAT. Clinical Opiate Withdrawal Scale measurements were performed pre and post OAT. Primary outcomes included pupil size in dark and bright illumination (mm). Latency of the pupillary light response (s), constriction and dilation velocity (mm/s), and percent constriction (%) were secondary outcomes.

Results: The mean predosing pupil size in dark and bright illumination was 4.33 ± 1.40 mm and 2.96 ± 0.79 mm, respectively. A significantly decreased mean pupil size was first detected at 15 minutes postdosing (4.01 ± 1.34 mm, $P = 0.0115$ for dark illumination; 2.71 ± 0.72 mm, $P = 0.0003$ for bright illumination) and this reduction in pupil size persisted at later postdosing timepoints. Those with Clinical Opiate Withdrawal Scale <5 after dosing had a greater decrease in dark pupil size ($10.6\% \pm 13.2$ vs $3.2\% \pm 3.2$, $P = 0.043$). There was no significant change in the remaining pupil reactivity parameters.

Conclusions: Automated pupillometry demonstrated a small but significant change in mean pupil size that occurred within 15 minutes of OAT dosing and was associated with low withdrawal scores. This pilot may inform future work to incorporate pupillometry measurement into OAT dosing assessments.

Key Words: opioid use disorder, opioid withdrawal, pupillometry

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The dosage of opioid agonist therapy (OAT) needed to control withdrawal symptoms varies widely based on an individual's history of opioid use and medical history. During the induction phase with methadone or buprenorphine therapy, treatment protocols typically begin with a standard loading dose and then provide incremental increases based on an individual's score on the Clinical Opiate Withdrawal Scale (COWS) or similar measure.[1,2] The COWS is a 48-point scale that assigns points to symptoms or signs of withdrawal including increased resting pulse rate, bone or joint aches, gastrointestinal upset, anxiety or irritability, restlessness, tremor, and pupillary dilation. A score from 5 to 12 represents mild withdrawal, 13 to 24 moderate withdrawal, 25 to 36 moderately severe withdrawal, and greater than 36 severe withdrawal.[2] Control of withdrawal symptoms is the first step in establishing a maintenance dose of OAT.[3] In addition, providers may use COWS or similar measurements to continue to titrate patients who are already on medication for OUD but who may be on a subtherapeutic dose, reporting continued cravings, withdrawal, or opioid use.

Though COWS and other similar instruments have been validated for use in quantifying opioid withdrawal, they rely on several inherently subjective measures that may lead to inaccurate dosing of OAT.[4] Under-treatment of OUD may result in persistent withdrawal symptoms and lingering cravings, increasing the risk of a return to opioid use. Overtreatment can cause sedation, respiratory depression, and, in the case of methadone therapy, prolongation of the QT interval and cardiac arrhythmia.[5–7] Improving the measurement of withdrawal with objective data, therefore, has the potential to improve treatment outcomes in OUD.

Resting pupil size is determined by the relative balance of dilating input – from the sympathetic nervous system,

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innervating the dilator pupillae muscle – to constricting input – from the parasympathetic nervous system, innervating the sphincter pupillae muscle. Opioid agonists trigger pupillary miosis primarily by blunting supranuclear inhibition of Edinger-Westphal neurons in the midbrain, pacemaker cells with a rapid intrinsic firing rate that drive parasympathetic constriction. The stress of opioid withdrawal, on the other hand, increases supranuclear inhibition to the Edinger-Westphal nucleus and overall sympathetic tone, driving pupillary dilation.[8,9]

Currently, the precision with which pupil size is measured in many clinical settings is low and prone to high interobserver variability.[10] In COWS, pupillary dilation is scored subjectively as "normal for room light," "possibly larger than normal for room light," "moderately dilated," and "so dilated that only a rim of iris is visible." Given normal, physiologic variation in resting pupil size from 1.5 to 7 mm, however, this "one-size-fits-all" approach may result in inaccurate scoring.[11,12] For example, patients with a larger baseline pupil size may be overscored while those with a smaller baseline pupil size may be underscored using the COWS approach.

More precise, objective measurements of an individual's pupil size and reactivity, as well as changes in these metrics following OAT dosing, could help eliminate interobserver variability and control for physiologic differences in resting pupil size between patients. In 1985, Higgins et al first suggested utilizing detailed pupil measurements, recorded in millimeters from magnified Polaroid photographs of eyes before and after a low-dose methadone challenge, to assess individual opioid tolerance.[13] More recently, several studies have taken advantage of automated pupillometers – devices that capture a short video of the eye and provide precise pupil measurements (Fig. 1) – to examine pupil size during spontaneous and naloxone-precipitated opioid withdrawal.[14–16] However, no studies to date have evaluated pupillometry measurements in a heterogenous sample of patients initiating or being titrating on a range of methadone or buprenorphine doses.

The aim of this pilot study is to determine whether there is a statistically significant change in pupil size and reactivity, measured to the hundredth millimeter using automated pupillometry, associated with adequate control of withdrawal

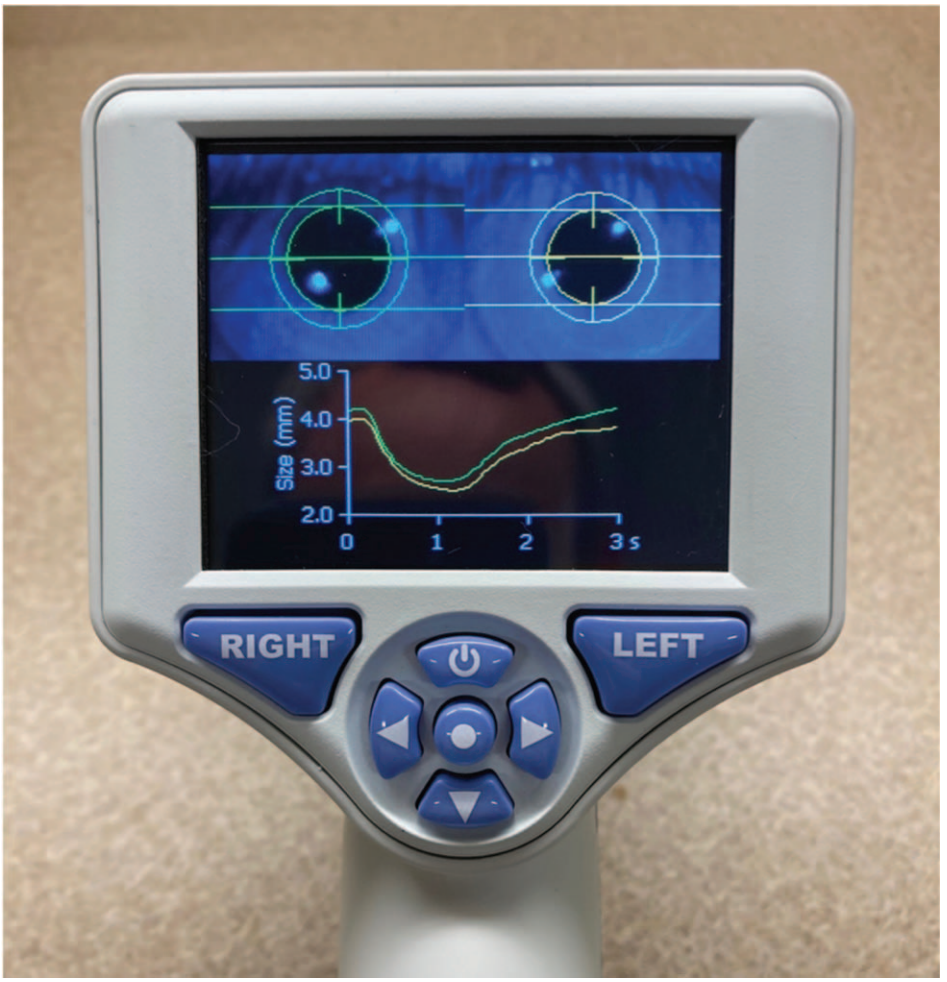

FIGURE 1. Sample automated pupillometry output showing an image of the right pupil (left side of the screen) and left pupil (right side of the screen) with a graph below plotting initial dark size at 0 seconds and reaction to a bright light stimulus over 3 seconds.

symptoms in a heterogenous convenience sample of patients receiving methadone or buprenorphine for OUD. We also aim to determine how quickly this change can be detected after administration of OAT.

METHODS

This prospective study was performed at an urban teaching hospital (Boston Medical Center, Boston MA) serving a wide range of patients from diverse backgrounds across New England. Written informed consent was obtained from all participants according to protocol, conforming to the tenets of the Declaration of Helsinki, and with approval from Boston Medical Center's institutional review board. Internal professional development funds from the Boston Medical Center Department of Ophthalmology were used to cover costs related to the pupillometry device.

Study Participants

Potential study participants included individuals age 18 to 50 who were admitted to Boston Medical Center (BMC) and for whom the inpatient Addiction Consult Service (ACS) was contacted to make recommendations on OAT for OUD. Both patients newly initiating medication for OUD and those already on treatment but requiring dose adjustments were eligible to participate. As part of the standard of care, all patients were interviewed by a member of the ACS to obtain a past medical history including details of substance use. Urine toxicology screening was performed to confirm opioid use and an expanded toxicology panel was obtained when clinically indicated by the primary medical team. Withdrawal symptoms were then measured using COWS (Supplemental Figure 1, http://links.lww.com/JAM/A238, page 7) and opioid agonist treatment was offered based on ACS assessment and patient preference, with dosing based on institutional protocol (Supplemental Figure 1, http://links.lww.com/JAM/A238).

Intervention and Outcome Measures

In addition to standard OUD therapy, study participants agreed to undergo several sets of automated pupillometry measurements using the NeurOptics NPi-200 pupillometer. To ensure uniform lighting conditions, all pupil measurements were obtained in an inpatient hospital room with overhead lights extinguished and shades drawn. Primary outcomes included pupil size in dark and bright illumination (mm). Pupil size in dark illumination was recorded under ambient lighting with the pupillometer's infrared camera. Bright light pupil size was recorded under standardized light stimulation from an LED on the pupillometry device (1000 lux). Secondary outcomes included latency of the pupillary light response (ie, time between delivery of a bright light stimulus and the first constriction movement of the pupil, measured in seconds), constriction and dilation velocity (mm/s), and percent constriction (%). All measurements were obtained from both eyes at 15 and 5 minutes before OAT and again at 5, 15, 30, and 60 minutes after OAT administration. COWS measurements were repeated 60 minutes after opioid agonist dosing. Study participants also agreed to have elements of their past medical history including ocular history, current medications, and substance use recorded in a secure database. Total, 24-hour OAT dosing received on the day of study participation was also recorded.

Statistical Analysis

To assess for differences in pupil size and reactivity between pre- and post-dosing measurements, we first generated descriptive statistics (mean, standard deviation, quantiles) for each pupillometry variable at each time point. Next, we used mixed linear models for each variable to evaluate the pattern of mean values over time as the primary analysis aim. Because pupillometry measurements were obtained in both eyes for each subject at each time point, side (right or left) was included as an independent variable in each model in addition to time. We treated both time and side as categorical, nominally scaled main effects. We tested for the interaction of time and side in initial models and, ruling out interaction, proceeded to fit main effects only models with time and side as factors. Based on the main effects only models, we calculated mean pupillometry values averaged over both sides. We employed a covariance structure of compound symmetry in all models and adjusted for multiple hypothesis testing using the Tukey-Kramer procedure for post hoc contrasts of specific time points subsequent to the finding of a significant main effect of time. We set a 2-sided alpha level of 0.05 throughout to determine statistical significance. We performed all analyses using SAS for Windows, version 9.4.

RESULTS

This study enrolled 27 patients between March and December 2018. Two patients who initially consented to participate decided to withdraw when study personnel returned to obtain pupillometry measurements – both reported feeling unwell as the reason to withdraw. The remaining 25 patients completed all pupillometry measurements (see Table 1 for patient demographics). All patients reported opioid use (confirmed on urine toxicology). Additionally, 20 of 25 participants had full urine toxicology screening performed with 11 (55%) testing positive for cocaine, 7 (35%) positive for benzodiazepine, 4 (20%) positive for amphetamine, and 4 (20%) positive for barbiturate.

At the time of pupillometry measurement, 18 patients had already received at least 1 dose of OAT for OUD and were having their dose further titrated, while 7 patients were initiating OAT for OUD. Nineteen patients received methadone treatment (mean dose 41.3 mg, range 10–80 mg) and 6 received buprenorphine-naloxone (all at 8 mg-2 mg). The mean COWS score was 3.56 ± 3.60 predosing and 1.32 ± 3.22 60 minutes postdosing. The majority of patients had good control of their withdrawal symptoms (score <5) at the postdosing COWS measurement, with only 2 patients continuing to score in the ''mild'' range (score 5–12) and 1 at the ''moderate'' level (score 13–24).

Primary Outcomes: Change in Pupil Size

To evaluate for any baseline (ie, pretreatment) fluctuations in pupil size and reactivity, we compared pupil measurements obtained at 15 and 5 minutes before opioid agonist administration. There was no statistically significant change

TABLE 1. Patient Demographics and Treatment Details

Parameter	Overall (N = 25)	% of Cohort
Age, yrs, (mean ± standard deviation)	34.6 ± 7.09	
Sex		
Female	7	28
Male	18	72
Ethnicity		
Hispanic/Latino	3	12
Non-Hispanic/Latino	22	88
Race		
American Indian/ Alaskan Native	1	4
Asian	1	4
Black/African American	1	4
Declined	4	16
White	18	72

Patient	Reason for Addiction Service Consult	Dose or Change
1	Dose evaluation	Methadone 30 -> 40 mg
2	Dose evaluation	Methadone 30 -> 40 mg
3	Dose evaluation	Methadone 40 -> 50 mg
4	Reinitiating treatment	Methadone 20 mg
5	Reinitiating treatment	Methadone 40 mg
6	Dose evaluation	Methadone 75 -> 80 mg
7	Dose evaluation	Methadone 20 -> 30 mg
8	Dose evaluation	Methadone 40 -> 55 mg
9	Reinitiating treatment	Buprenorphine 8 mg
10	Dose evaluation	Buprenorphine 8 mg
11	Dose evaluation	Methadone 45 -> 50 mg
12	Dose evaluation	Methadone 40 -> 50 mg
13	Initiating treatment	Methadone 20 mg
14	Reinitiating treatment	Methadone 40 mg
15	Reinitiating treatment	Methadone 40 mg
16	Dose evaluation	Methadone 40 mg
17	Dose evaluation	Methadone 20 -> 30 mg
18	Reinitiating treatment	Buprenorphine 8 mg
19	Dose evaluation	Buprenorphine 4 -> 8 mg
20	Dose evaluation	Methadone 64 mg
21	Dose evaluation	Buprenorphine 8 mg
22	Dose evaluation	Methadone 50 -> 55 mg
23	Dose evaluation	Methadone 40 -> 50 mg
24	Dose evaluation	Buprenorphine 8 mg
25	Dose evaluation	Methadone 65 -> 70 mg

in any of the mean pupil size or reactivity parameters between these 2 time points.

The mean dark pupil size obtained 5 minutes before dosing was 4.33 mm (SD, 1.40 mm; range, 2.04–7.26 mm). When compared to this predosing value, no significant change was noted at the first postdosing measurement (5 minutes after), though a significantly decreased mean pupil size (4.01 mm; SD, 1.34 mm; range, 2.14–6.82 mm) was noted at the 15-minute postdosing measurement ($P = 0.0115$). The difference increased and remained statistically significant over subsequent postdosing measurements (Fig. 2). When comparing dark pupil measurements at 5 minutes pre- and 60 minutes post-dosing, the average decrease in size was 10.6% ± 13.2 for the well-controlled patients with COWS <5 (N = 22) and 3.2% ± 3.2 for the patients who continued to have a score ≥5 on COWS (N = 3) ($P = 0.043$).

The mean bright light pupil size obtained 5 minutes before dosing was 2.96 mm (SD, 0.79 mm; range, 1.67–4.89 mm). As with dark size, no significant change from this predosing value was noted at the first postdosing measurement (5 minutes after), but a significantly decreased mean pupil size (2.71 mm; SD, 0.72 mm; range, 1.48–4.07 mm) was detected at the 15-minute postdosing measurement ($P = 0.0003$). The difference increased and remained statistically significant over subsequent postdosing measurements (Fig. 3). When comparing bright light pupil measurements at 5 minutes pre- and 60 minutes post-dosing, the average decrease in size was 9.5% ± 12.6 for the well-controlled patients (N = 22) and 5.7% ± 9.9 for the patients who continued to have a score ≥5 on COWS (N = 3); however, this did not reach statistical significance ($P = 0.59$).

Secondary Outcomes: Changes in Pupil Reactivity

Of the remaining pupillary parameters measured – latency, constriction velocity, percent constriction from dark to bright illumination, and dilation velocity – there was no significant change in mean values when comparing measurements from 5 minutes before dosing and any postdosing time point (see Table 2 for full pupillometry results).

DISCUSSION

In this study, we show that there is a small but statistically significant change in mean pupil size detectable by automated pupillometry within 15 minutes of OAT administration in a heterogenous cohort of patients with OUD receiving methadone or buprenorphine. In addition, patients whose withdrawal symptoms were well-controlled had a significantly greater change in dark pupil size 60 minutes after OAT dosing compared with those who continued to score ≥5 on COWS. These findings suggest there may be a threshold change in pupil size corresponding to adequate symptom control, making pupillometry a potentially useful objective measure of withdrawal and its response to treatment. Also, the wide range of pupil sizes at baseline and the subtle but significant changes noted suggest that pupillometry may add refinement to the more subjective COWS measure.

Though changes in pupil size with OAT dosing appear to have clinical utility, our data did not show a significant change in measures of pupil reactivity. These findings make sense when considering the physiology of the pupil. As discussed in the introduction, resting pupil size is directly impacted by opioids and the stress of opioid withdrawal. Pupil reactivity measures such as latency and constriction velocity, on the other hand, evaluate the function of the pupillary light reflex arc. Within this reflex pathway, input regarding light intensity travels along the optic nerve and tracts (ie, the afferent limb) and a corresponding pupillary constriction response occurs via the parasympathetic fibers that travel with cranial nerve III (ie, the efferent limb). While injury to the afferent or efferent limbs of this pathway can affect the pupillary light response, OAT would not be expected to affect transmission speed or pupil reactivity given the absence of opioid receptors within this loop.

The association between the COWS score and changes in pupil size following OAT dosing suggest that pupillometry could play a role as either an adjunctive measure to the

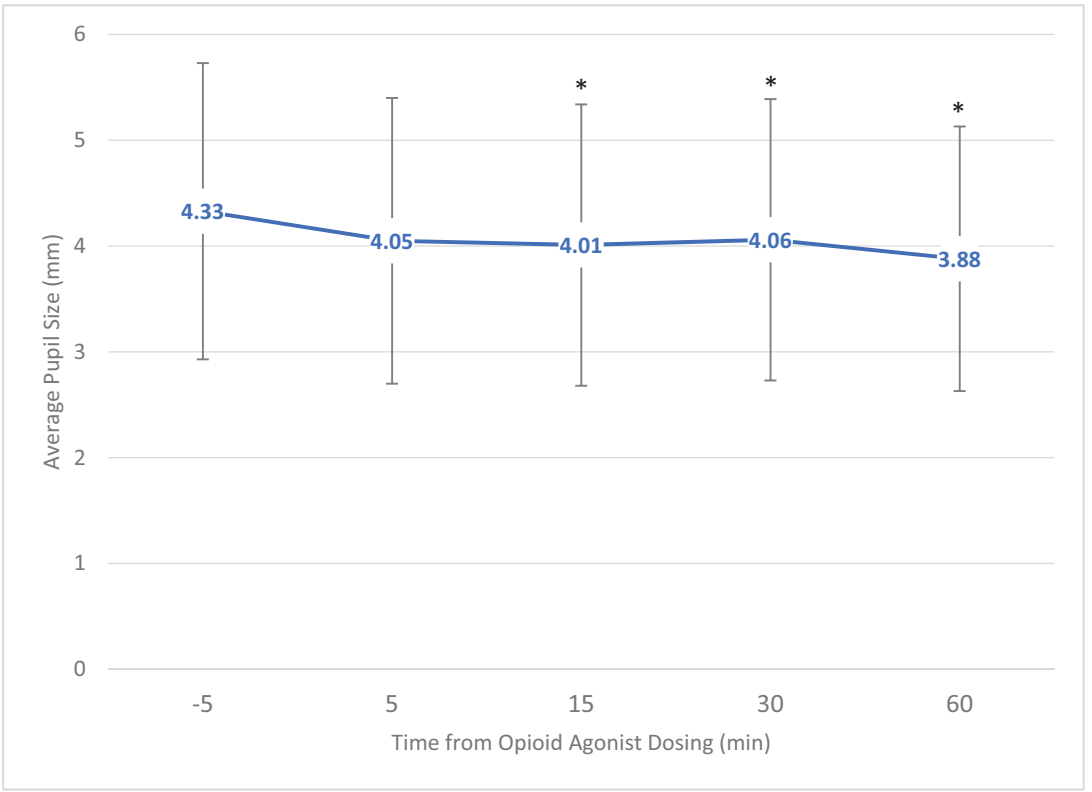

FIGURE 2. Average dark size pupil measurements (N = 50). Error bars represent one standard deviation above and below the mean. An asterisk represents a significant ($P < 0.05$) change in mean pupil size compared to the –5 minute (baseline) measurement.

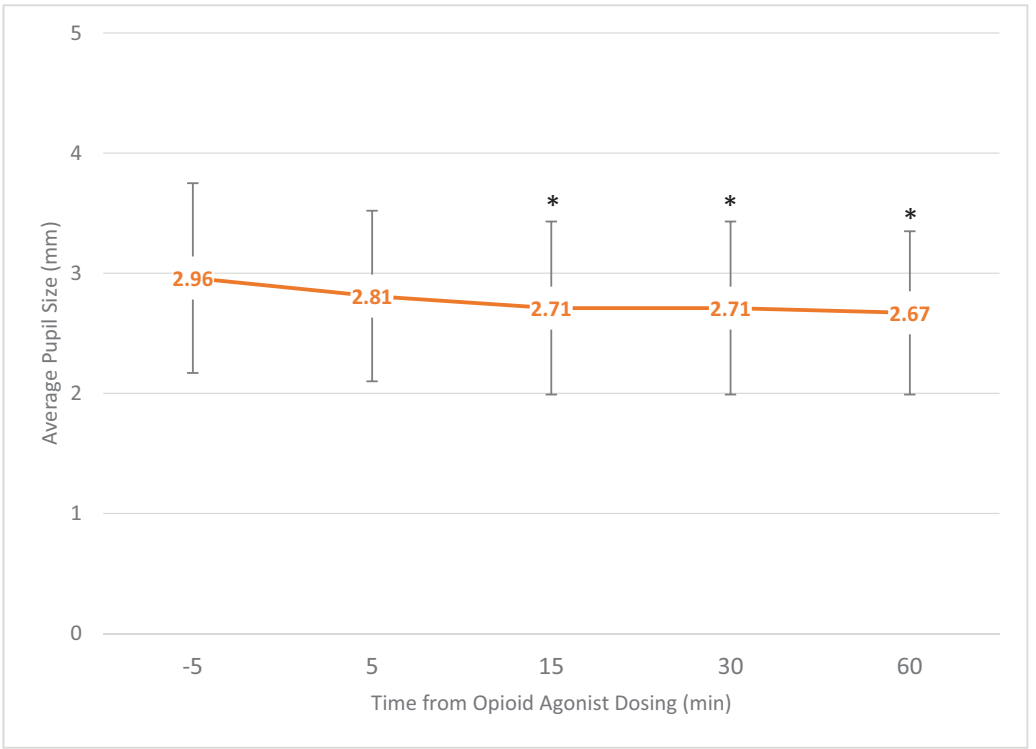

FIGURE 3. Average bright light size pupil measurements (N = 50). Error bars represent one standard deviation above and below the mean. An asterisk represents a significant ($P < 0.05$) change in mean pupil size compared to the –5 minute (baseline) measurement.

TABLE 2. Pupillometry Results (N = 50)

Parameter (mean ± SD)	Time From Opioid Agonist Dosing (min)				
	−5	5	15	30	60
Dark Size (mm)	4.33 ± 1.40	4.05 ± 1.35	4.01 ± 1.34* ($P = 0.0115$)	4.06 ± 1.33* ($P = 0.0047$)	3.88 ± 1.25* ($P < 0.0001$)
Bright Size (mm)	2.96 ± 0.79	2.81 ± 0.71	2.71 ± 0.72* ($P = 0.0003$)	2.72 ± 0.72* ($P < 0.0001$)	2.68 ± 0.68* ($P < 0.0001$)
Percent Constriction	30.1 ± 8.1	28.6 ± 8.0	30.5 ± 8.8	31.4 ± 9.2	29.5 ± 8.3
Latency (s)	0.23 ± 0.04	0.23 ± 0.03	0.23 ± 0.03	0.23 ± 0.04	0.23 ± 0.03
Constriction Velocity (mm/s)	2.19 ± 0.80	2.15 ± 0.86	2.20 ± 0.93	2.39 ± 0.96	2.12 ± 0.82
Dilation Velocity (mm/s)	1.00 ± 0.42	1.00 ± 0.40	1.04 ± 0.45	1.03 ± 0.44	0.92 ± 0.37

*A significant ($P < 0.05$) change compared to −5 minute (baseline) measurement.
N = number of eyes completing the analysis, SD = standard deviation.

traditional COWS or as part of a training program to help improve reliability of the COWS. Even though some patients in the cohort were not experiencing even mild withdrawal symptoms before dosing (COWS <5), all of these patients were believed to require additional medication by an addiction specialist, highlighting the limitations of the COWS. Given the subjective nature of COWS, it is highly time intensive to train bedside nursing staff to use the COWS and many nurses may use this scale inconsistently or feel that they have inadequate education. Prior work on nurse education for the COWS has demonstrated a need for simulation sessions to obtain confidence and consistency with the scale as well as careful testing and retesting to obtain reliability.[17,18]

Training to use a pupillometer, on the other hand, takes a matter of minutes. Pupillometry devices are already in widespread use by nursing staff in critical care settings with a high level of inter-observer reliability.[19] Additionally, several free or inexpensive pupillometry smartphone applications have recently been released with comparable functionality to inpatient devices that could potentially be employed in outpatient treatment centers with minimal cost. Pupillometry could therefore be useful as a clinical support tool for nurses or other health care providers performing the COWS. Pupillometry alone could also be validated in future work as an alternative measure to the COWS in certain clinical settings.

A handful of prior studies have employed careful measurements of the pupil in patients with OUD. In 1985, Higgins et al compared pupil size, measured from magnified Polaroid photographs, before and 120 minutes after a 40 mg methadone challenge in a cohort of 28 heroin users undergoing treatment for OUD.[13] This study found a significant negative correlation between the average dollar value of reported heroin use in a week and the amount of pupillary constriction 2 hours after methadone dosing, suggesting that the degree of opioid-induced miosis is a function of individual tolerance. In our study, we accounted for individual tolerance by allowing variable OAT dosing based on past opioid use and initial COWS scoring. As a result, the majority of patients in our cohort ended up with good control of withdrawal symptoms and a uniform pupillary response.

A more recent automated pupillometry study in naloxone-precipitated withdrawal by Bergeria et al provides additional data that are complementary to our findings.[14] In this cohort of 95 patients with OUD, pupil size and scores from COWS and the self-reported Subjective Opiate Withdrawal Scale (SOWS) were recorded before and at regular intervals after a 0.4 mg intramuscular dose of naloxone. Before naloxone administration, a smaller resting pupil size was associated with lower-scoring on COWS and SOWS. Peak pupil size after naloxone administration was associated with increases in SOWS scores. Similar to our study, a significant change in pupil size – in this case, dilation – was detected within 15 minutes of administration of the opioid reversal agent. Two earlier studies, using more rudimentary pupillometry techniques in patients undergoing spontaneous opioid detoxification over several days, report a significant increase in pupil size in one cohort and equivocal changes in the other.[15,16]

Strengths and Limitations

The strengths of this study include a prospective design and a cohort that closely mirrors the demographics of OUD patients in both Massachusetts, where the study was performed, and the US as a whole.[20,21] To increase the generalizability of our findings, the sample included patients on either methadone or buprenorphine as well as patients who had already received at least 1 dose of medication during their hospitalization. The inclusion criteria were broad and allowed for enrollment of participants using other medications with the potential to affect pupil size and reactivity. This also represents a potential limitation, however, as our sample size was not large enough to conduct subgroup analyses of changes in pupil size based on past ocular or medical history, type of medication for OUD, or use of other substances or prescribed medications that could influence pupil size.

Another potential limitation is that the mean pretreatment COWS score in our cohort (3.56, less than the cutoff of 5 corresponding to ''mild'' withdrawal) suggests that many of the study participants were already fairly well-controlled before OAT dose adjustment during their hospitalization. However, the fact that we were able to detect a significant change in pupil size even in this fairly well-controlled population, along with the finding of a greater size change in those patients with post-treatment COWS <5, speaks to a high level of sensitivity afforded by automated pupillometry measurements.

The large number of comparisons for each pupil measure across multiple time points represents another potential limitation – specifically, that a statistically significant change from the reference time point could be detected purely by chance. To control for this, we adjusted our *P*-values for multiple comparisons using the Tukey-Kramer procedure as described in the methods section.

One final limitation relates to the fact that 2 of the 27 patients who initially consented to participate in the study withdrew before having pupillometry measurements recorded. Both reported feeling unwell due to withdrawal symptoms and wished to avoid any unnecessary interactions with research staff. Though this could theoretically limit the feasibility of automated pupillometry in patients experiencing more severe withdrawal symptoms, obtaining pupillometry measurements is no more time consuming or invasive than the currently-employed subjective pupil size evaluation performed as part of COWS.

Future studies should focus on a larger population to determine what confounding variables exist that could distort the accuracy of pupillometry. Future work should also include more patients with more severe opioid withdrawal symptoms (ie, COWS >5) – this will allow us to better identify the threshold change in pupil size between suboptimal and adequate symptom management.

CONCLUSIONS

Dosing of OAT for the treatment of OUD varies widely based on individual tolerance and relies heavily on subjective measures of withdrawal. At our institution, we are fortunate to have physicians who are board-certified in addiction medicine to provide expert care to patients with OUD and nurses who are comfortable managing this patient population. However, much of the United States is still working to establish the necessary infrastructure to address the burgeoning demand for OUD treatment, particularly outside of urban centers.[22–24] Using automated pupillometry, we report that there is a small but significant change in pupil size detected soon after OAT dosing that is associated with good control of withdrawal symptoms. With future study, we hope that this objective measure can help to train or empower additional healthcare providers to manage opioid withdrawal and improve outcomes among patients with OUD.

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