Exploring automated pupillometry in comparison to the Withdrawal Assessment Tool-1 for the evaluation of opiate abstinence syndrome in pediatric critical care patients.

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Abstract

Research Question: In pediatric critical care patients tolerant to opiates, is automated pupillometry more sensitive in detecting opiate abstinence syndrome when compared to the gold standard observational scoring system?

Background: Opiates are often used in the Pediatric Intensive Care Unit to maintain analgesia and sedation. In doing so, pediatric patients quickly develop tolerance to opiates and must be slowly tapered off to avoid inducing opiate abstinence syndrome. Currently, the gold standard to evaluate for opiate abstinence syndrome is the Withdrawal Assessment Tool-1 (WAT-1), which is a 12-point subjective scale monitoring for symptoms of opiate withdrawal. There are currently no objective tools to evaluate for opiate abstinence syndrome in children. This study attempts to evaluate if automated pupillometry is an accurate and reliable tool to objectively evaluate for opiate abstinence syndrome in pediatric patients who are tolerant to opiates and undergoing an opiate taper. Since opiates are parasympathetic agonists, they stimulate pupillary constriction. Further, it has been shown that pupillary constriction develops tolerance similarly to the analgesic and euphoric tolerance. It is not until the opiate dose is manipulated that patients who are tolerant to opiates will show a change in pupil diameter. Therefore, it is reasonable to assume that automated pupillometry could accurately and reliably evaluate for opiate abstinence syndrome by objectively measuring pupillary changes as the patient tapers off opiates.

Materials and Methods: Opiate-tolerant patients in the pediatric intensive care unit were enrolled in this study. Data was collected twice daily. The WAT-1 scale was collected first, and then automated pupillometry was performed. The right eye was utilized to collect data on the pupillary light response, while the left eye was utilized to collect data on pupillary unrest without a light stimulus.

Results: Five patients were enrolled. Ages ranged from infancy to 10 years. Each automated pupillometry variable was correlated to total daily opiate dose, using Spearman's rho correlation. WAT-1 scores were also correlated to total daily opiate dose and to each automated pupillometry variable using Spearman's rho correlation. Of the limited data, the only significant findings were correlations between total daily opiate dose and initial pupil diameter ($p=0.01$) in Subject 2, total daily opiate dose and maximum constriction velocity ($p=0.01$) in Subject 2, and total daily opiate dose and pupillary unrest in Subject 4 when removing the last two time points ($p=0.03$). However, when analyzing Subject 4's total duration on study, pupillary unrest did not significantly correlate to total daily opiate dose ($p=0.16$). Remaining data did not produce statistically significant correlations when p-value was set to $\alpha<0.05$.

Conclusions: This exploratory study revealed some statistically significant correlations between automated pupillometry and total daily opiate dose, and no statistical significance between automated pupillometry and WAT-1 scores or between WAT-1 scores and total daily opiate dose. Therefore, the current study revealed automated pupillometry may be more sensitive to opiate abstinence syndrome when compared to the gold standard WAT-1 scoring system. However, limitations included small sample size, difficulty of device to capture pupils when surrounded by dark-colored irises, and difficulty of using device on subjects who were agitated while tapering off sedation. Future studies may examine use of ultrasound to measure pupil size.

Research Question

In pediatric critical care patients tolerant to opiates, is automated pupillometry more sensitive in detecting opiate abstinence syndrome when compared to the gold standard observational scoring system?

Currently, the gold standard for evaluating opiate abstinence syndrome in pediatric patients is the Withdrawal Assessment Tool-1 (WAT-1), which is a subjective scale noting the presence of signs or symptoms of opiate withdrawal in the last 12 hours. There are currently no objective tools to measure opiate abstinence syndrome in pediatric patients.

Since opiates are parasympathetic agonists, they stimulate pupillary constriction. Therefore, it is reasonable to assume that an objective tool such as automated pupillometry could evaluate for opiate abstinence syndrome, noting pupillary changes as the patient tapers off opiates.

Introduction

Opiates are often used in the pediatric intensive care unit (PICU) to maintain analgesia and sedation. In doing so, pediatric patients quickly develop tolerance (1). Thus, patients must be slowly tapered off opiates to avoid inducing an opiate abstinence syndrome (1). Common pediatric opiate abstinence syndrome features include agitation, high-pitched cry, tremors, pupil dilation, hallucinations, fever, sweating, yawning, sneezing, hypertension, tachycardia, tachypnea, poor feeding, vomiting and diarrhea (2). As the opiates are tapered down, the patient's symptoms are assessed by several subjective scales, such as the Withdrawal Assessment Tool (WAT-1) (3). Currently, there are no objective tools or devices to monitor opiate abstinence syndrome in pediatric patients.

In neonates who were exposed to opiates in utero, modified versions of the Finnegan Neonatal Abstinence Scoring System are used to assess opiate abstinence syndrome in the neonatal intensive care unit (NICU) (4). These scales are observational in design and quantify the severity of the Neonatal Abstinence Syndrome (NAS) (5). If a patient scores above the threshold, opiate therapy is started to treat the abstinence syndrome. These scales are specific for the wide range of symptoms experienced in NAS, but they are limited in their ability to expand beyond the neonatal population.

Therefore, the Withdrawal Assessment Tool (WAT-1) was adapted to monitor opiate abstinence syndrome in the remaining pediatric patients in intensive care (3). The WAT-1 is performed twice a day as patients taper off opiates (3). The assessment includes 1) loose stools in the last 12 hours, 2) vomiting in the last 12 hours, 3) temperature >38C in the last 12 hours, 4) state (asleep, awake, calm, distressed), 5) tremor, 6) sweating, 7) uncoordinated/repetitive movement, 8) yawning or sneezing, 9) startle to touch, 10) muscle tone, and 11) time to gain calm state after stimulus (3). Total score ranges from 0-12 (3). The WAT-1 is valid and comprehensive in monitoring opiate abstinence syndrome in pediatric patients and is currently the gold standard for monitoring comfort and sedation in pediatric patients tapering off opiates (3). However, the WAT-1 is still a subjective scale and relies on potentially inaccurate or unreliable observation by the clinician.

Despite these scoring systems being widely implemented in pediatric intensive care units across the country, they have significant limitations. Most importantly, these scales rely on subjective observation. This leads to challenges with inter-rater reliability because the caregiver population that assesses opiate abstinence syndrome is typically large and heterogeneous, including intensivist, nurses, pharmacist, etc. Additionally, the opiate tapering regimen is typically long in duration. Therefore, even in well-trained populations, there is still a risk for low inter-rater reliability throughout the opiate tapering process.

To our knowledge, there are no true objective scales that can be used to monitor opiate abstinence syndrome in pediatric critical care patients. Our goal is to examine if automated hand-held pupillometry is equivalent and/or superior to the WAT-1 in measuring opiate abstinence syndrome in pediatric patient critical care patients.

Pupillometry Innervation and Action

Historically, pupillometry was a subjective examination whereby the clinician estimated pupil size by holding a ruler to the patient's eye to measure diameter. More recently, automated pupillometry was developed to objectively measure pupil diameter and reactivity (6).

Pupillary constriction (miosis) and dilation (mydriasis) require an intricate balance between the parasympathetic and sympathetic branches of the autonomic nervous system (7). When bright light is directed into one eye, sensory neurons on the retina detect this light stimulus and generate an action potential. The axons from these sensory neurons converge to form the optic nerve (Cranial Nerve II). The temporal fibers of the optic nerve travel ipsilaterally to the pretectal nuclei in the midbrain. The nasal fibers of the optic nerve decussate at the optic chiasm and travel to contralateral pretectal nuclei. The signal then splits and synapses with bilateral Edinger-Westphal (E-W) nuclei. The preganglionic parasympathetic fibers arise from the E-W nuclei and travel along the oculomotor nerve (Cranial Nerve III) to the ciliary ganglion. The postganglionic parasympathetic efferent fibers ultimately innervate the sphincter pupillae muscles of both irises, stimulating bilateral pupil constriction. Therefore, bilateral pupil constriction occurs when light is originally directed at one eye (7-9).

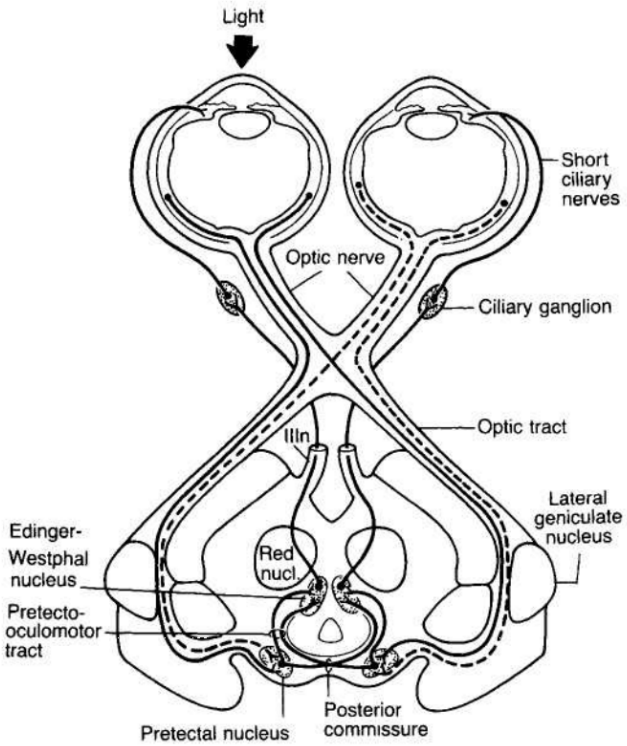

Figure 58.1
Neuroanatomy of the light reflex.

Photo: Spector, 1990

The sympathetic nervous system in turn, stimulates mydriasis. The preganglionic sympathetic fibers arise from the upper thoracic spinal cord (T1-T2) and travel along the sympathetic trunk until they synapse at the superior cervical ganglion, lateral to the C1 and C2 cervical vertebrae

(8). The postganglionic sympathetic fibers enter the orbit and ultimately innervate the dilator pupillae, causing mydriasis (8).

Thus, when one system is suppressed, the other dominates (7). An example of this is seen with Horner syndrome, which results from a lesion along the sympathetic pathway (10). The symptoms of Horner syndrome include ptosis, anhidrosis, and miosis on the affected side of the face (10). This is to be expected since sympathetic stimulation normally causes mydriasis. Hence, a lesion disrupting the sympathetic stimulation would result in miosis, or parasympathetic dominance.

Opiates and Pupillometry

Pupillary constriction and dilation can also be manipulated by certain xenobiotics, such as opiates. Opiates are parasympathetic agonists, and therefore stimulate miosis (11). Opiates bind to the mu, kappa, and delta receptors, inhibiting GABA release from the presynaptic neuron (11). With GABA inhibited, the postsynaptic neuron can release dopamine, serotonin, and norepinephrine (11). These neurotransmitters mediate the analgesic and reward pathways seen in opioid addiction (11). Several studies have indicated that the pupillary constriction mechanism develops tolerance similarly to the analgesic and euphoric tolerance seen in opioid dependence (12-16). Thus, patients who are tolerant to opiates will have normal pupil diameter. It is not until the opiate dose is manipulated that the patient will show a change in pupillary diameter (13,14).

Methadone is a mu-opiate agonist, frequently used to medicate patients who are being tapered off opiates (17). The apparent elimination half-life of methadone is quite long, but ranges widely between 15-60 hours, with a median of about 24 hours (17). Considering normal pharmacokinetic principles, clinicians observe that in many opiate-dependent patients, methadone often reaches steady state plasma concentrations and physiological effects within 2-5 days (17). The oral bioavailability for methadone is also high and ranges from 70-80%, with parenteral to enteral administration considered 1:1 (17). Methadone undergoes hepatic metabolism by CYP3A4 and is excreted renally (17). Since methadone is an opiate agonist, it also stimulates pupillary constriction.

It has been shown that automated pupillometry is effective in evaluating opiate abstinence syndrome in tolerant adults (18). Adults with DSM-IV classified opioid dependence were experimentally treated with naloxone, an opiate reversal agent, and subsequent automated pupillometry and subjective withdrawal scales were performed (18). There was a significant correlation between peak pupillary diameter, as measured by automated pupillometry, and the Subjective Opiate Withdrawal Scale during naloxone administration (18). This study suggests that automated pupillometry can objectively evaluate opioid dependence and withdrawal in adults. However, no studies have investigated this phenomenon in pediatric patients.

In pediatric patients, automated hand-held pupillometry has been used to quantify pain and neurological insult. One study found a significant correlation between self-reported pain, as measured by the Visual Analogue Scale (VAS), and maximum pupil constriction velocity, as measured by the NeurOptics PLR-100 infrared pupillometer (19). In addition, automated pupillometry has been used to measure increased intracranial pressure due to neurological injury

in pediatric patients (20). However, no studies have examined pupillometry as a method to measure opiate abstinence syndrome in pediatric patients. It is also important to note that there does not appear to be a correlation between pupil size and age (21). Thus, there is no apparent age effect in pupillary function, as measured by pupillometry (21).

The present study used the NeurOptics PLR-3000 Pupillometer (NeurOptics, Inc., Irvine, CA) to measure opiate tolerance and abstinence syndrome in pediatric patients during a methadone tapering regimen (22). This handheld device emits an infrared light stimulus to evoke a pupillary response and has built-in algorithms to control for the natural hippus of the pupil. The device measures maximum pupil diameter before constriction (mm), minimum pupil diameter during peak constriction (mm), average constriction velocity (mm/sec), maximum constriction velocity (mm/sec), latency (sec), average dilation velocity (mm/sec), and time to recover to 75% of initial diameter (sec). Further, the PLR-3000 measures a novel, exploratory variable named "pupil unrest", which is the baseline continuous fluctuation of the pupil in ambient light (22, 30). The clinical model of this device (NPi-200) has been shown to produce accurate, rapid, non-invasive, and safe pupillary assessments in both children and adults (20, 21, 23-28). The research model (PLR-3000) used in the study was expected to produce the same results with no known additional safety concerns, when used by trained research investigators.

Pupillary unrest is the continuous oscillation of the pupil in ambient light (also denoted as PUAL in the literature) (31,32). The mechanism underlying pupillary unrest is thought to be due to the opposing sympathetic and parasympathetic systems at the Edinger-Westphal nuclei (31,32). Previous studies have shown that pupillary unrest is depressed by both general anesthesia (33) and opioids (34,35). More specifically, decline in pupillary unrest was dose-dependent on opioid exposure in subjects who were opiate-naive (34). Further, pupillary unrest has been significantly correlated with post-operative pain scores (30). Therefore, it was hypothesized that in our patient population of pediatric critical care patients tolerant to opiates, pupillary unrest would increase as the opiate dose decreased.

Materials and Methods

This exploratory pilot study investigated the use of a medical device (PLR-3000) in comparison to the standard-of-care scoring system (WAT-1) in pediatric critical care patients.

Patient Population: Five pediatric patients admitted to the Pediatric Intensive Care Unit (PICU) at Cook Children's Medical Center were enrolled in the study.

Inclusion criteria included patients admitted to the PICU who were opiate-tolerant, ready for opiate tapering, and who were either individually or by legally authorized representative able to understand and consent to study procedures. Exclusion criteria included patients whose pupillary light reflex was not fully intact on at least one side, who were receiving other topical, systemic, or aerosolized drugs known to affect the pupillary light reflex (i.e. topical β-blockers, aerosolized atropine), who suffered sufficient trauma to the face wherein the primary investigator determined the use of the PLR-3000 would be unsafe or cause pain, who were receiving opiates for end-of-life palliative care, or who were unable or unwilling to provide written informed consent or assent.

Subjects enrolled in the study underwent opiate tapering as determined by their clinical team. The current study did not influence or interfere with the patient's tapering regimen, but rather collected data as the opiate tapering ensued.

WAT-1: The Withdrawal Assessment Tool-1 (WAT-1) is a subjective scale used to evaluate opiate withdrawal symptoms, which is used in the pediatric critical care setting as standard of care for opiate tapering. The WAT-1 is typically completed twice daily, and the total score can range from 0-12.

The WAT-1 evaluation began with a chart review of any loose/watery stool in the last 12 hours, any vomiting/wretching/gagging in the last 12 hours, and any temperature >38C in the last 12 hours. Then, the evaluator observed the subject for 2 minutes and assessed their state (asleep/awake/calm or awake/distressed), presence of a tremor, presence of sweating, presence of uncoordinated or repetitive movements, and presence of yawning or sneezing. Then, the evaluator performed a 1-minute stimulus observation, noting if there was a startle after a glabellar tap and if muscle tone felt normal or increased. Lastly, the evaluator noted the number of minutes required for the subject to regain their calm state.

Automated Pupillometry: The NeurOptics PLR-3000 is a handheld automated pupillometer that records pupillary changes both at baseline and in response to light. Each subject had their own SmartGuard, which attached to the front of pupillometer device and stored the subject's data with a built-in microchip. The SmartGuard was labelled with the subject's medical record number sticker and remained at their bedside for the duration of the study. Once the subject's participation in the study concluded and the de-identified data was downloaded to an excel spreadsheet, the SmartGuard was destroyed. The PLR-3000 device, charging station, and SmartGuards were obtained through a no-cost research loan from NeurOptics, Inc.

The primary investigator and research assistant were trained on use of the PLR-3000 before conducting data collection on subjects.

The PLR-3000 had the dual capability of recording pupillary changes in response to a light stimulus, in addition to the exploratory variable of pupillary unrest at baseline, without a light stimulus. For this study, the pupillary light reflex (PLR) was measured in the right eye, while pupillary unrest was measured in the left eye. For PLR in the right eye, the device was programmed to emit a light stimulus and then record the pupillary changes for a duration of 3 seconds. The device recorded maximum pupil diameter before constriction (mm), minimum pupil diameter during peak constriction (mm), average constriction velocity (mm/sec), maximum constriction velocity (mm/sec), latency (sec), average dilation velocity (mm/sec), and time to recover to 75% of initial diameter (sec). The screen lit up in a green color if the variables were collected accurately and in a red color if the variables were not collected accurately. For example, if the subject blinked continuously throughout the 3 seconds, if the device was unable to locate the pupil, or if the device was removed from the subject's eye before the 3 seconds were complete, the screen would illuminate in red. If necessary, the PLR was repeated up to three times as to ensure the subject's tolerability was not jeopardized. After the PLR variables were collected, the investigator switched the device to the pupillary unrest settings. For pupillary unrest, the PLR-3000 was programmed to simply record the pupil at baseline for 5 seconds without a light stimulus. After the 5 seconds, the device produced a video of the pupil, a graph and value indicating pupillary unrest, and a standard deviation value.

Methods: Patients in the PICU were screened by the primary investigator (PI) utilizing the inclusion and exclusion criteria. Once deemed eligible, the PI and research assistant approached the patient and guardian to discuss the study and assess their interest. If interested, the PI and research assistant completed the official consent and/or assent process with the patient and guardian.

Each subject was given a randomized six-digit identification number, which was used to label the data collection sheets and subject folders. The data collection sheets were kept in separate folders for each subject and stored in a locked, badge-access room in the PICU. Each subject was also given their own SmartGuard for the automated pupillometry device, which was labelled with their hospital medical record number (MRN) sticker and kept at their bedside. The SmartGuard was labelled with the MRN to ensure the clinical staff kept the SmartGuard with the patient if the patient was to move rooms.

Subjects were assessed twice daily for the duration of their enrollment on the study. The WAT-1 was performed first so as not to be influenced by the automated pupillometry stimulus. After the WAT-1 was recorded, the investigator collected the automated pupillometry data, performing PLR on the right eye and pupillary unrest on the left eye. Either the bedside nurse or a second investigator would assist with automated pupillometry by using two cotton swabs to roll the upper and lower eyelids open if the subject was sedated and/or unable to follow commands. Each eye was attempted up to three times if necessary.

Automated pupillometry data (identified by the randomized six-digit subject ID number) was transferred via Bluetooth directly from the handheld device to an excel spreadsheet on a secure,

password protected research laptop. WAT-1 data were transferred from data collection sheets to a secure REDCap database. Lastly, subject demographics (age, sex, race, dosing weight), total opiate doses, and primary diagnosis were pulled from their electronic medical record and recorded in REDCap under their randomized six-digit subject ID number.

ANALYSIS/STATISTICS:

Due to the exploratory nature of the study, the data from each subject was analyzed individually to assess whether there were any significant correlations between total daily opiate dose, WAT-1 scores, and/or pupillometry values. Data was non-linear and therefore the Spearman's Rho (also known as the Spearman's Rank Correlation Coefficient) with a p-value set to $\alpha < 0.05$ was utilized to determine statistical significance.

Results

This exploratory pilot study investigated the use of automated pupillometry in comparison to the Withdrawal Assessment Tool-1 to evaluate opiate abstinence syndrome in pediatric critical care patients. Due to the nature of the study design, each subject acted as their own control. Therefore, results are published in a case series format.

Subject 1

Subject 1 was a Caucasian male infant admitted to the PICU for respiratory failure due to bronchiolitis. He was enrolled on study for a total of four days, with six total data collection sessions (Table 1). However, due to the continuous inability of the device to measure this subject's pupillary changes, this subject was removed from the study, and statistical analysis was not performed on data collected for assumption that data was inaccurate.

Table 1. Automated pupillometry data for Subject 1.

Day*	Pupillary Unrest (AU)	Initial Pupil Diameter (mm)	End Pupil Diameter (mm)	Pupil Latency (sec)	Avg Pupil Constriction Velocity (mm/sec)	Max Pupil Constriction Velocity (mm/sec)	Pupil Dilation Velocity (mm/sec)	Time to reach 75% (sec)
1b	1.4	1.7	1.1	0.3	-0.55	-1.24	0.61	0.94
2a	1.5	1.4	1.1	0.23	-0.84	-1.24	NA	NA
2b	1.6	10	10	NA	NA	-1.37	NA	NA
3a	1.5	6.5	1.3	0.43	-3.77	-21.95	NA	NA
3b	1.2	7.6	NA	NA	NA	NA	NA	NA
4a	7.6	10	0.5	0.17	-56.85	-56.85	NA	NA

*Day noted as "a" to delineate morning and "b" to delineate afternoon data collection.

Subject 2

Subject 2 was a 10-year-old male admitted to the PICU for traumatic brain injury post motor vehicle collision. He was enrolled on study for a total of three days, with five total data collection sessions (Table 2). Total daily opiate dose ranged from 27.20 - 27.25 morphine milligram equivalents. Pupillary unrest ranged from 3.7-6.5 arbitrary units. Initial pupil diameter before light stimulus ranged from 4.7-6.5mm. End pupil diameter after light stimulus ranged from 2.2-4.1mm. Pupil latency after light stimulus ranged from 0.13-0.9 seconds. Average pupil constriction velocity after light stimulus ranged from -1.22 to -25.52 mm/sec. Max pupil constriction velocity after light stimulus ranged from -2.9 to -37.39 mm/sec. Pupil dilation velocity ranged from 0.68 to 3.88mm/sec, with two instances of device unable to calculate value. Device was only able to calculate one instance of time to reach 75% of baseline pupil diameter (0.37 sec), and therefore this value was not included in statistical analysis.

Each automated pupillometry value was compared to total daily opiate dose. Spearman's rho was calculated for each comparison to determine if a statistically significant correlation between the values existed. Total daily opiate dose was significantly correlated to initial pupil diameter ($p=0.01$) and maximum constriction velocity ($p=0.01$). There was no statistically significant correlation between total opiate daily dose and the remaining pupillometry values. WAT-1 scores were unable to be obtained and therefore were not included.

Table 2. Total daily opiate dose and automated pupillometry data for Subject 2

Day*	Total Daily Opiate Dose (MME)	Pupillary Unrest (AU)	Initial Pupil Diameter (mm)	End Pupil Diameter (mm)	Pupil Latency (sec)	Average Pupil Constriction Velocity (mm/sec)	Max Pupil Constriction Velocity (mm/sec)	Pupil Dilation Velocity (mm/sec)	Time to Reach 75%
1a	27.25	4	5.1	4.1	0.23	-1.22	-2.9	0.68	NA
1b	27.25	3.7	4.7	3.8	0.23	-2.37	-3.42	0.82	NA
2a	27.21	4.9	6.2	2.2	0.13	-5.06	-21.6	NA	NA
2b	27.21	6.5	5.7	3.9	0.17	-1.3	-4.64	3.88	0.37
3a	27.2	5.7	6.5	3.2	0.9	-25.52	-37.39	NA	NA

*Day noted as "a" to delineate morning and "b" to delineate afternoon data collection.

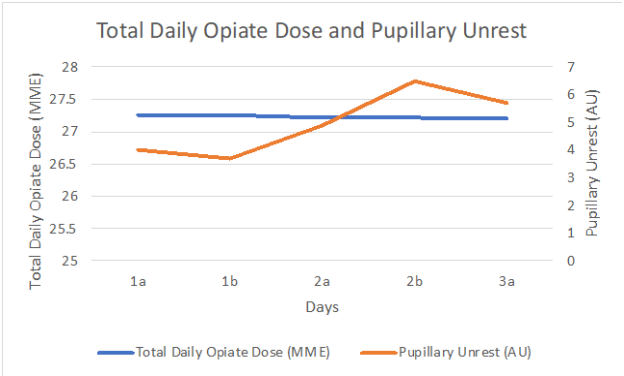

Figure 1. Total Daily Opiate Dose and Pupillary Unrest
r_s = -0.79057, p (2-tailed) = 0.11137

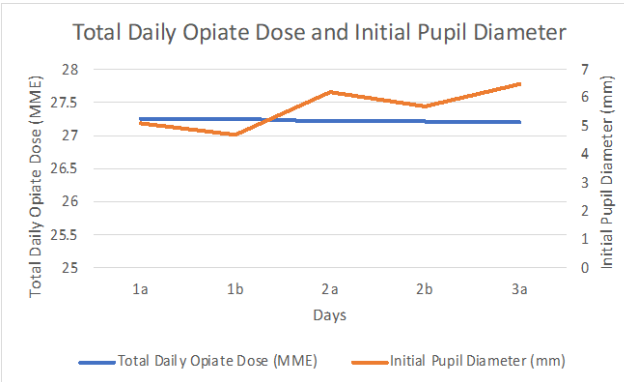

Figure 2. Total Daily Opiate Dose and Initial Pupil Diameter
r_s = -0.94868, p (2-tailed) = 0.01385.

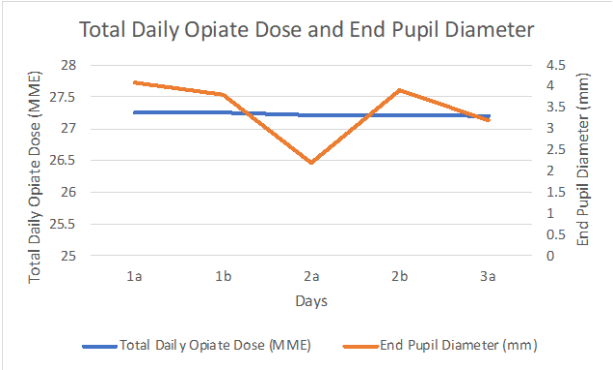

Figure 3. Total Daily Opiate Dose and End Pupil Diameter
r_s = 0.57975, p (2-tailed) = 0.30557.

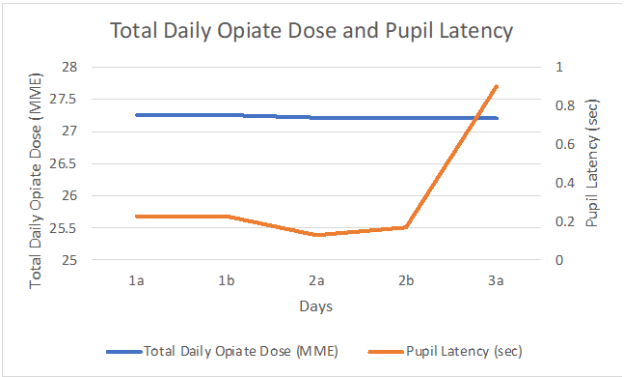

Figure 4. Total Daily Opiate Dose and Pupil Latency
r_s = -0.10815, p (2-tailed) = 0.86257.

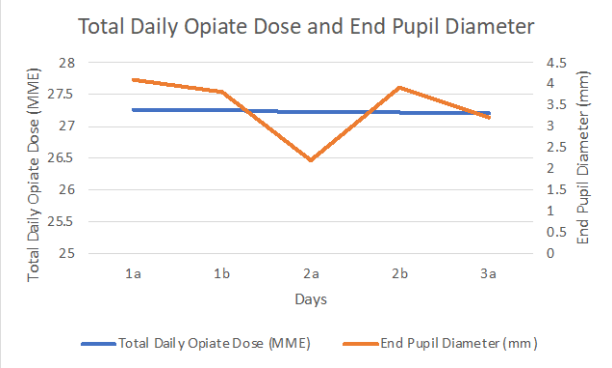

Figure 5. Total Daily Opiate Dose and End Pupil Diameter
r_s = 0.73786, p (2-tailed) = 0.15462.

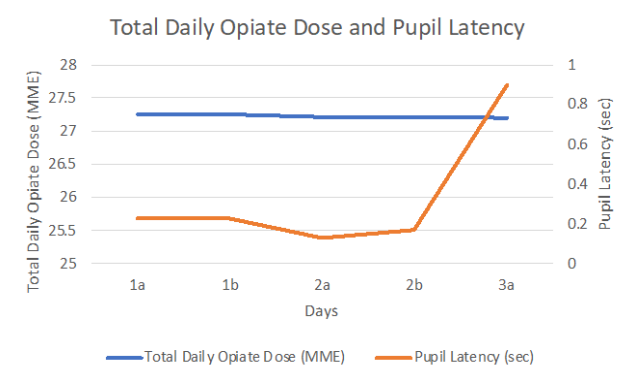

Figure 6. Total Daily Opiate Dose and Pupil Latency
r_s = -0.10815, p (2-tailed) = 0.86257.

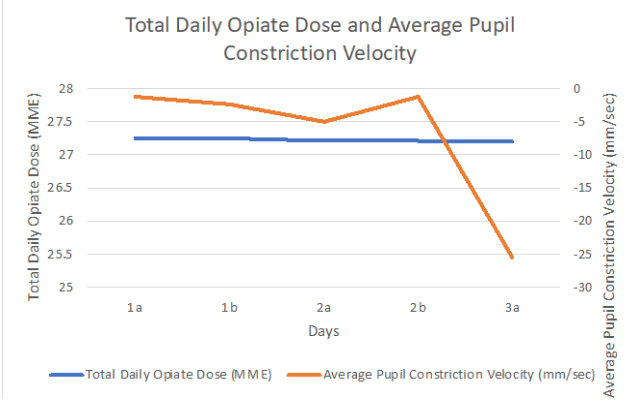

Figure 7. Total Daily Opiate Dose and Average Pupil Constriction Velocity
r_s = 0.73786, p (2-tailed) = 0.15462.

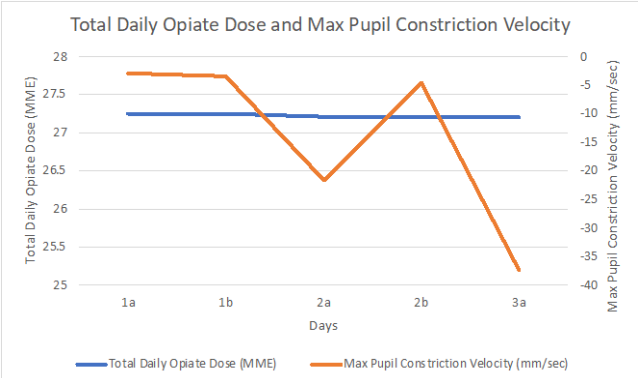

Figure 8. Total Daily Opiate Dose and Max Pupil Constriction Velocity
r_s = 0.94868, p (2-tailed) = 0.01385.

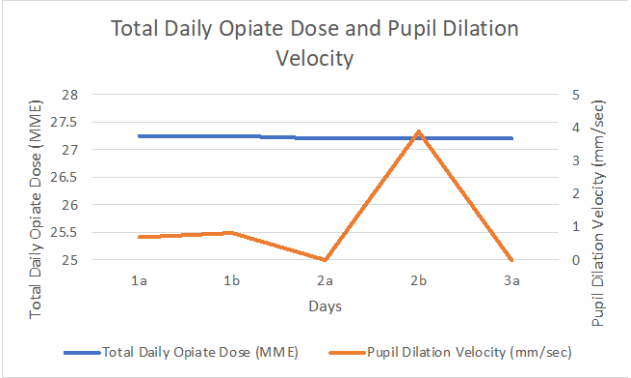

Figure 9. Total Daily Opiate Dose and Pupil Dilation Velocity
r_s = 0.45963, p (2-tailed) = 0.4361.

Subject 3

Subject 3 was a 9-year-old female admitted to the PICU for autoimmune encephalitis and new onset refractory status epilepticus. She was enrolled on study for a total of 35 days, with 45 total

data collection sessions (Table 3). Total daily opiate dose ranged from 24.097-100.44105 morphine milligram equivalents. WAT-1 score ranged from 0-4. Pupillary unrest ranged from 2.2-7.4 arbitrary units. Initial pupil diameter before light stimulus ranged from 2.3-7.0mm. End pupil diameter after light stimulus ranged from 0.5-5.3mm. Pupil latency after light stimulus ranged from 0.13-0.37 seconds. Average pupil constriction velocity after light stimulus ranged from -1.08 to -3.92 mm/sec. Max pupil constriction velocity after light stimulus ranged from -1.35 to -15.6 mm/sec. Pupil dilation velocity after peak constriction ranged from 0.35 to 3.1 mm/sec. Time for pupil to reach 75% of baseline diameter ranged from 0.67 to 1.87 seconds. However, pupil was only able to reach 75% of baseline diameter 41.3% of the time.

Each automated pupillometry value was compared to total daily opiate dose and to WAT-1 score. In addition, WAT-1 score was compared to total daily opiate dose. Of note, the automated pupillometry variable “time to reach 75%” was not included in statistical analysis because it was unable to be calculated more than 50% of the time. Spearman’s rho was calculated for each comparison to determine if a statistically significant correlation between the values existed. For subject 3, there were no statistically significant correlations between pupillometry values, WAT-1 scores, and total daily opiate dose.

Table 3. Total daily opiate dose, WAT-1 score, and automated pupillometry data for Subject 3

Day*	Total Daily Opiate Dose (MME)	WAT-1 Score	Pupillary Unrest (AU)	Initial Pupil Diameter (mm)	End Pupil Diameter (mm)	Pupil Latency (sec)	Avg. Pupil Constriction Velocity (mm/sec)	Max Pupil Constriction Velocity (mm/sec)	Pupil Dilation Velocity (mm/sec)	Time to reach 75%
1b	24.0975	4	5.9	6.1	5	0.37	-1.09	-3.45	0.87	NA
2a	24.0975	1	5.3	5.4	4.3	0.23	-1.5	-2.12	0.95	1.87
2b	24.0975	2	5.9	5.9	3.9	0.2	-2.21	-6.31	NA	NA
3a	40.1092	1	5.8	5.5	4.8	0.2	-1.1	-1.66	0.85	0.87
3b	40.1092	1	2.3	2.4	1.9	0.27	-1.19	-1.75	0.75	0.77
4b	42.1131	1	3.2	3	2.2	0.27	-1.81	-2.47	0.99	0.74
5a	42.1313	0	6.2	5.8	4.3	0.23	-1.79	-3.1	1.61	NA
6a	48.1365	1	4.7	5.3	3.4	0.23	-2.89	-5.04	1.48	1.64
6b	48.1365	1	5.2	4.6	3	0.2	-3.05	-4.36	1.82	0.94
7a	48.1365	1	5.3	6	4.1	0.23	-2.87	-4.56	1.32	NA
7b	48.1365	1	2.5	2.3	1.9	0.23	-1.08	-1.35	0.35	0.97
8a	48.1131	1	5.4	5.2	3.2	0.27	-2.37	-4.48	1.57	1.6
8b	48.1131	2	2.2	2.4	1.8	0.27	-1.21	-1.83	0.66	0.77
9a	72.1092	1	5.9	5.8	3.6	0.3	-2.29	-5.34	1.86	1.44
9b	72.1092	0	5.5	5.5	3.8	0.27	-2	-2.36	1.24	NA
10a	64.1053	1	5.3	4.6	2.9	0.23	-2.12	-3.69	1.88	NA
10b	64.1053	0	4.1	2.4	1.9	0.23	-1.74	-2.27	0.83	1.1
11b	56.0936	1	4.7	5.7	3.4	0.23	-2.89	-4.7	1.5	NA
12b	72.1053	2	5.3	5.2	4.1	0.27	-1.64	-2.69	1.38	0.9
13a	56.0936	2	5.9	5.9	3.4	0.27	-3.51	-4.94	1.39	NA
13b	56.0936	2	5.4	5.7	3.3	0.2	-2.84	-6.03	1.72	NA
14a	48.1014	1	5.2	4.5	3.4	0.23	-2.6	-3.66	1.01	0.94
14b	48.1014	1	5.2	5.3	3.7	0.2	-2.74	-4.04	1.35	NA
15a	72.1014	2	5.2	3.8	2.4	0.3	-1.64	-3.03	1.04	NA
15b	72.1014	3	4.8	4.9	3.4	0.17	-2.3	-4.75	1.51	1.44
16a	56.1014	2	5.3	5.4	3.5	0.23	-2.49	-4.55	1.92	1.7
16b	56.1014	2	5	5	3.3	0.2	-2.62	-4.41	1.74	NA
17a	48.1131	2	5.6	5.6	3.6	0.23	-2.54	-4.29	1.62	NA
17b	48.1131	3	5.9	6.1	3.8	0.2	-2.83	-3.89	2.02	NA
18b	48.1365	1	5.8	5.3	3.2	0.2	-2.52	-5.66	0.78	NA
19a	36.1053	1	5.7	6.7	4.4	0.27	-2.68	-3.64	1.5	NA
20a	48.0975	0	5.8	5.9	5.1	0.27	-1.73	-2.47	0.71	NA
20b	48.0975	0	6	5.9	5.1	0.27	-1.73	-2.47	0.71	NA
21a	42	0	N/A	6.9	0.5	0.2	-3.92	-15.6	N/A	NA
21b	42	0	5.6	7	5	0.13	-2.18	-4.05	1.77	1.5
22a	70	2	5.9	6.5	4.4	0.27	-2.69	-4.63	N/A	NA
22b	70	N/A	6.4	6	4	0.23	-2.7	-4.53	1.84	NA
23a	56	1	6.8	6.7	4.9	0.3	-2.17	-3.03	1.82	1.5
23b	56	1	5	5.3	3.3	0.2	-2.54	-4.84	1.93	NA
24a	42	1	7.1	5.9	4.2	0.37	-1.75	-3.92	3.1	0.67
24b	42	1	7.4	N/A	N/A	N/A	N/A	NA	N/A	NA
25a	57.2	1	4.3	4.2	2.7	0.23	-2.97	-4.51	0.94	NA
26a	57.6	1	6.1	6.4	4.8	0.13	-1.42	-8.88	1.5	0.74
26b	57.6	0	6.1	6.7	5.3	0.27	-1.76	-2.68	0.92	NA
27b	57.6	0	7.3	6.5	4.8	0.23	-2.03	-3.47	1.95	NA
28a	57.6	1	6.9	6.6	4.6	0.23	-2.55	-3.89	1.74	NA

*Day noted as “a” to delineate morning and “b” to delineate afternoon data collection.

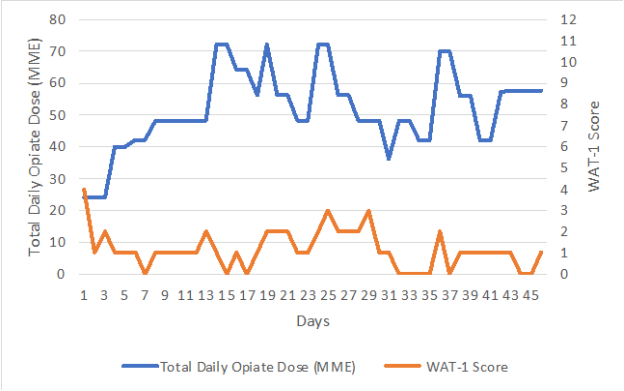

Figure 10. Total Daily Opiate Dose and WAT-1 Score
r_s = 0.09497, p (2-tailed) = 0.5349.

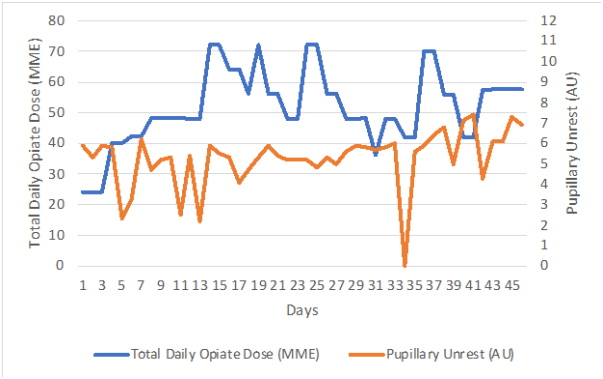

Figure 11. Total Daily Opiate Dose and Pupillary Unrest
r_s = -0.04281, p (2-tailed) = 0.78006.

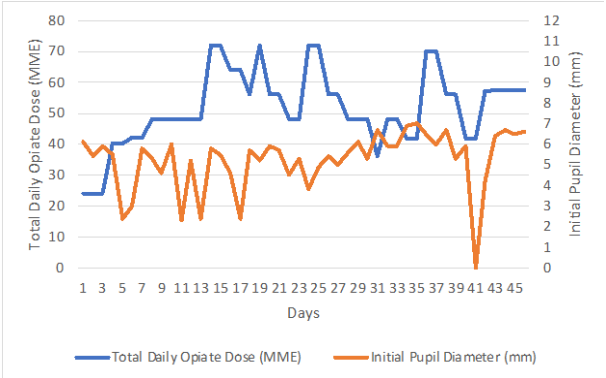

Figure 12. Total Daily Opiate Dose and Initial Pupil Diameter
r_s = -0.11503, p (2-tailed) = 0.45177.

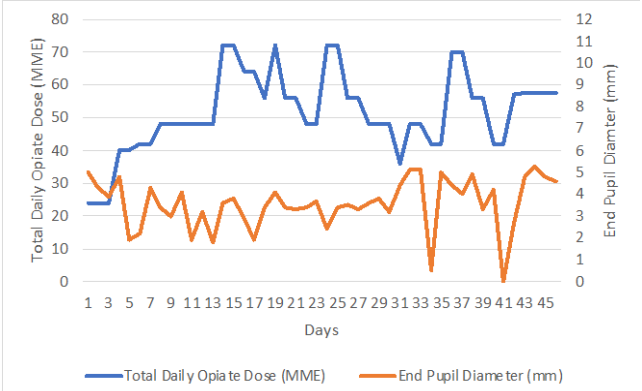

Figure 13. Total Daily Opiate Dose and End Pupil Diameter
r_s = -0.12353, p (2-tailed) = 0.41882.

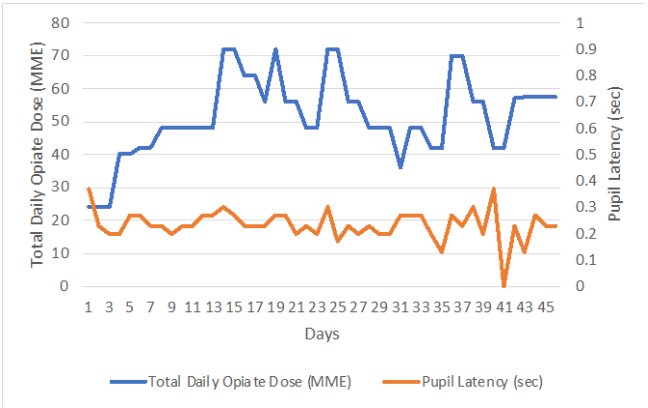

Figure 14. Total Daily Opiate Dose and Pupil Latency
r_s = 0.05036, p (2-tailed) = 0.74249.

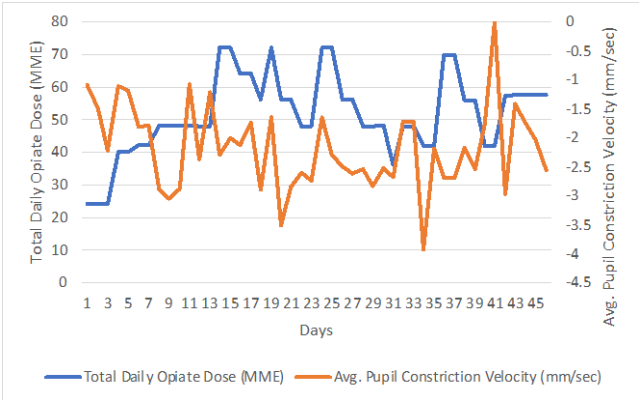

Figure 15. Total Daily Opiate Dose and Average Pupil Constriction Velocity
r_s = -0.14639, p (2-tailed) = 0.33726.

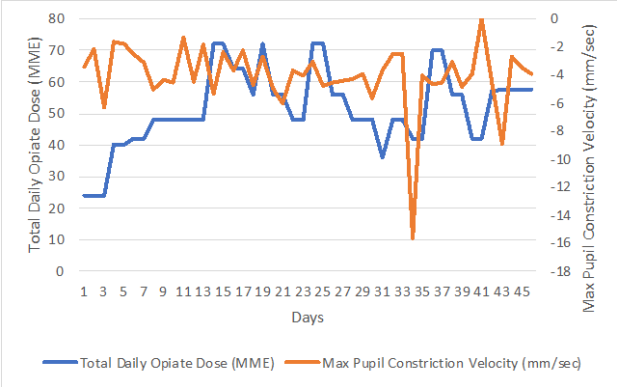

Figure 16. Total Daily Opiate Dose and Max Pupil Constriction Velocity
r_s = -0.19919, p (2-tailed) = 0.18959.

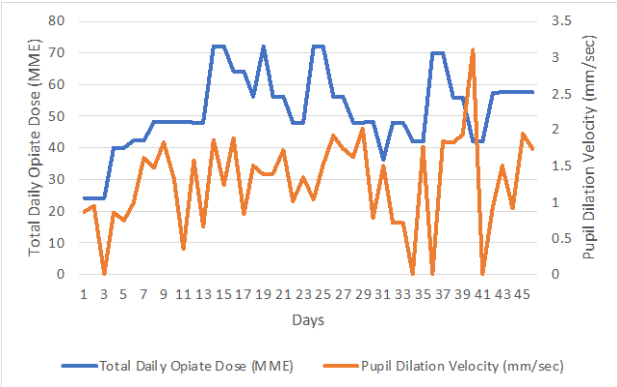

Figure 17. Total Daily Opiate Dose and Pupil Dilation Velocity
r_s = 0.26908, p (2-tailed) = 0.08486.

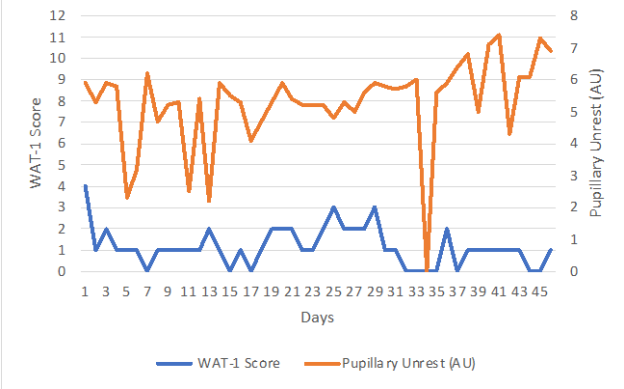

Figure 18. WAT-1 Score and Pupillary Unrest
r_s = -0.16115, p (2-tailed) = 0.29602.

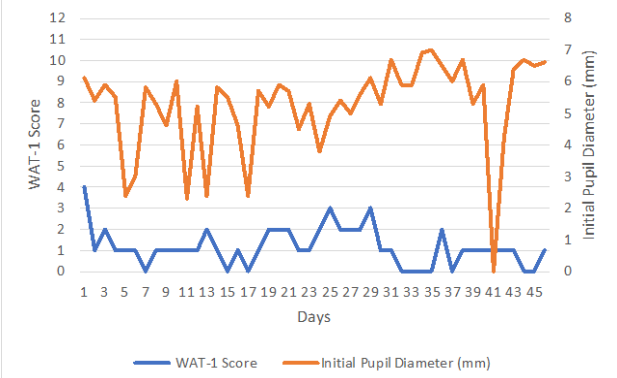

Figure 19. WAT-1 Score and Initial Pupil Diameter
r_s = -0.19389, p (2-tailed) = 0.20726.

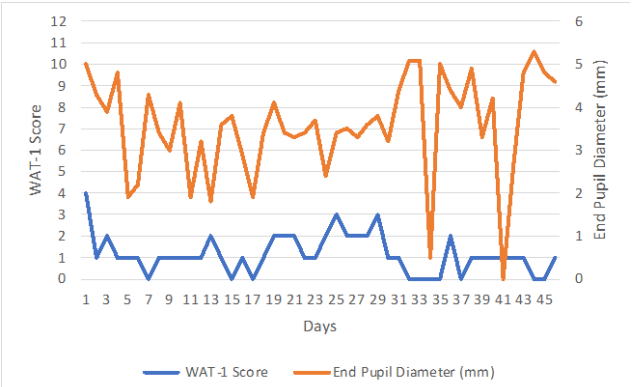

Figure 20. WAT-1 Score and End Pupil Diameter
r_s = -0.1882, p (2-tailed) = 0.22116.

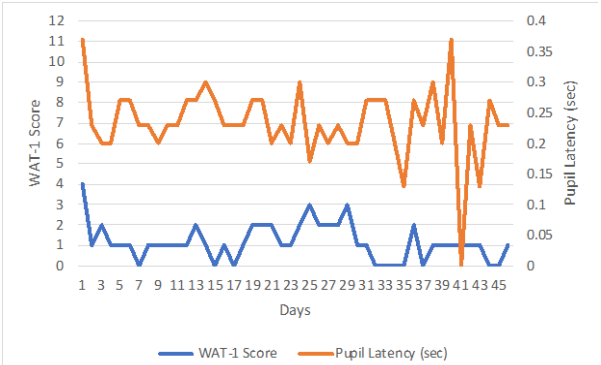

Figure 21. WAT-1 Score and Pupil Latency
r_s = -0.0041, p (2-tailed) = 0.97894.

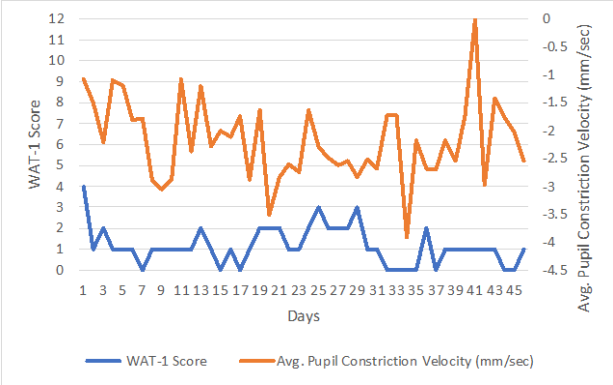

Figure 22. WAT-1 Score and Average Pupil Constriction Velocity
r_s = -0.12013, p (2-tailed) = 0.43733.

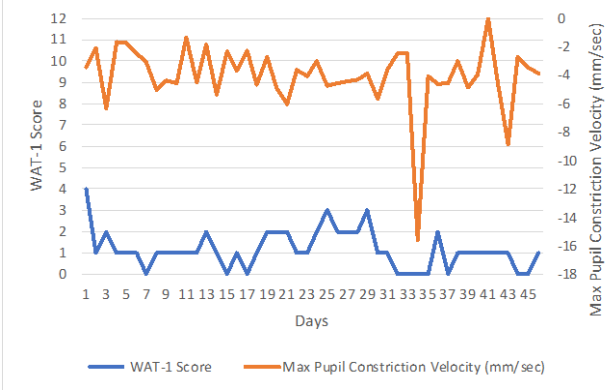

Figure 23. WAT-1 Score and Max Pupil Constriction Velocity
r_s = -0.25956, p (2-tailed) = 0.08886.

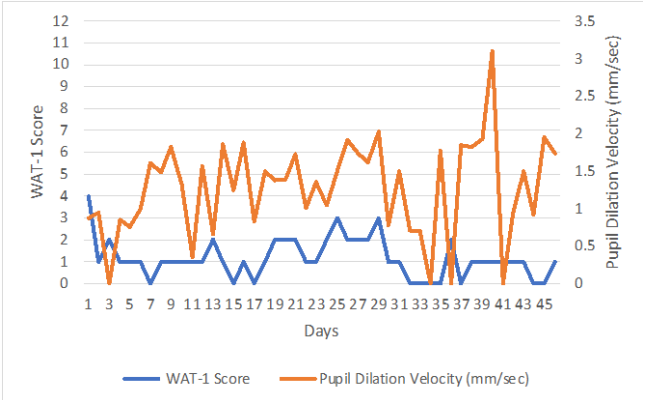

Figure 24. WAT-1 Score and Pupil Dilation Velocity
r_s = 0.16049, p (2-tailed) = 0.31618.

Subject 4

Subject 4 was an 8-year-old female admitted to the PICU for a traumatic brain injury. She was enrolled on study for a total of six days, with eight total data collection sessions (Table 4). Total daily opiate dose ranged from 3.4-12 morphine milligram equivalents. WAT-1 score ranged from 0-1. Pupillary unrest ranged from 5.0-7.5 arbitrary units. Initial pupil diameter before light stimulus ranged from 3.2-6.6mm. End pupil diameter after light stimulus ranged from 2.5-4.2mm. Pupil latency after light stimulus ranged from 0.13-0.3 seconds. Average pupil constriction velocity after light stimulus ranged from -4.84 to -2.02 mm/sec. Max pupil constriction velocity after light stimulus ranged from -2.39 to -8.23 mm/sec. Pupil dilation velocity after peak constriction ranged from 1.11 to 2.06 mm/sec, with one reading unable to produce a dilation velocity. Time for pupil to reach 75% of baseline diameter ranged from 0.77-1.77 seconds. However, pupil was only able to reach 75% of baseline diameter 37.5% of the time.

Each automated pupillometry value was compared to total daily opiate dose and to WAT-1 score. In addition, WAT-1 score was compared to total daily opiate dose. Of note, the automated pupillometry variable "time to reach 75%" was not included in statistical analysis because it was

unable to be calculated more than 50% of the time. Spearman's rho was calculated for each comparison to determine if a statistically significant correlation between the values existed. For subject 4, there were no statistically significant correlations between pupillometry values, WAT-1 scores, and total daily opiate dose. However, when plotting total daily opiate dose and pupillary unrest onto a graph (Figure 26) it was noted that the graphs mirrored one another for the first six time points. Spearman's rho was calculated for this period and was found to be significant (r_s=-0.85, p=0.03).

Table 4. Total daily opiate dose, WAT-1 score, and automated pupillometry data for Subject 4

Day*	Total Daily Opiate Dose (MME)	WAT-1 Score	Pupillary Unrest (AU)	Initial Pupil Diameter (mm)	End Pupil Diameter (mm)	Pupil Latency (sec)	Avg. Pupil Constriction Velocity (mm/sec)	Max Pupil Constriction Velocity (mm/sec)	Pupil Dilation Velocity (mm/sec)	Time to reach 75% (sec)
1a	9.9128	0	5.7	5.5	3.1	0.23	-3.5	-5.61	NA	NA
2a	8.8258	1	7.5	6.6	4	0.2	-3.39	-5.8	1.59	NA
2b	8.8258	0	7.4	6.6	4.2	0.13	-3.03	-4.78	1.61	NA
3a	12	1	5	5.5	2.9	0.2	-4.84	-8.23	2.06	1.77
3b	12	1	5.1	4.5	2.8	0.23	-2.49	-4	1.52	1.24
4a	6.8	0	7.4	6.2	3.6	0.3	-2.68	-5.74	1.63	NA
5a	5.1	0	6.5	3.2	2.5	0.2	-2.02	-2.39	1.59	0.77
6b	3.4	0	6.2	6.5	3.9	0.23	-3.25	-4.54	1.11	NA

*Day noted as "a" or "b" to delineate morning (a) versus afternoon (b) data collection.

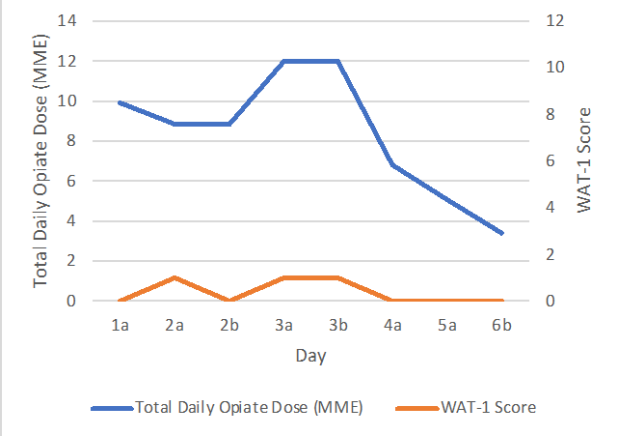

Figure 25. Total Daily Opiate Dose and WAT-1 Score
r_s = 0.68432, p (2-tailed) = 0.0612

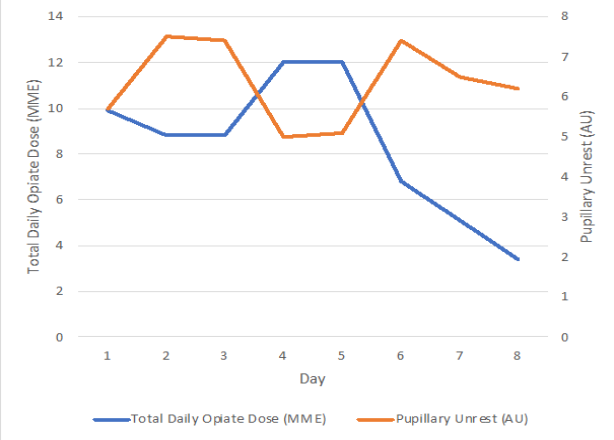

Figure 26. Total Daily Opiate Dose and Pupillary Unrest
r_s = -0.55153, p (2-tailed) = 0.15646.
r_s = -0.85084, p (2-tailed) = 0.03171 when eliminating last 2 time points

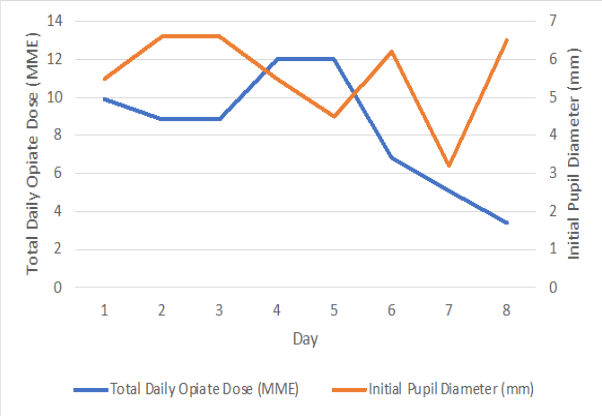

Figure 27. Total Daily Opiate Dose and Initial Pupil Diameter
r_s = -0.22561, p (2-tailed) = 0.59112.

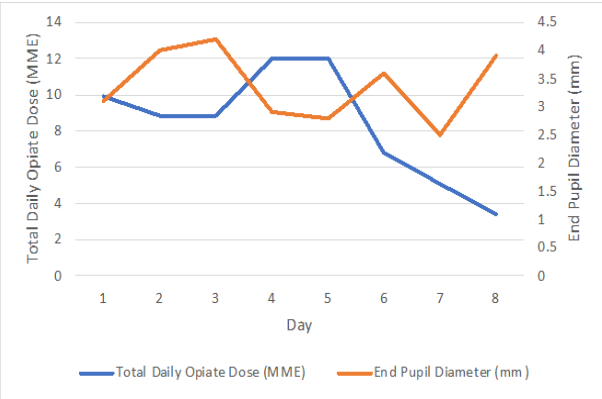

Figure 28. Total Daily Opiate Dose and End Pupil Diameter
r_s = -0.24098, p (2-tailed) = 0.56535.

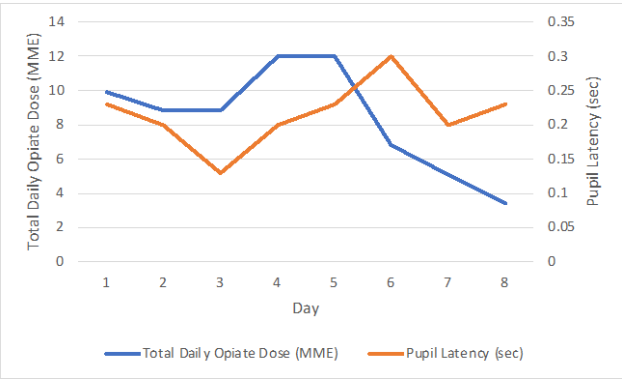

Figure 29. Total Daily Opiate Dose and Pupil Latency
r_s = -0.11401, p (2-tailed) = 0.78808.

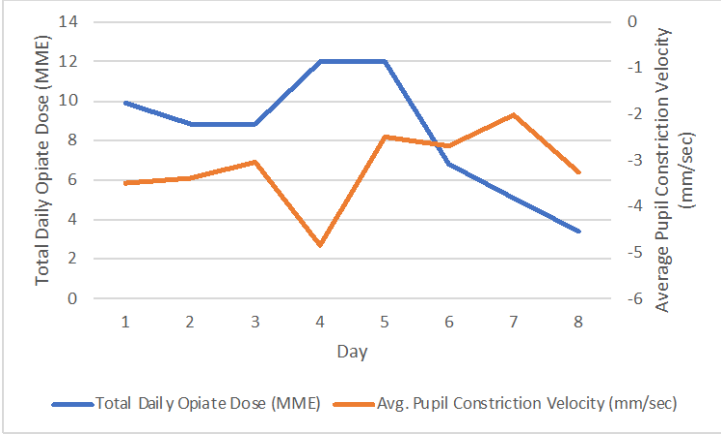

Figure 30. Total Daily Opiate Dose and Average Pupil Constriction Velocity
r_s = -0.38557, p (2-tailed) = 0.34551.

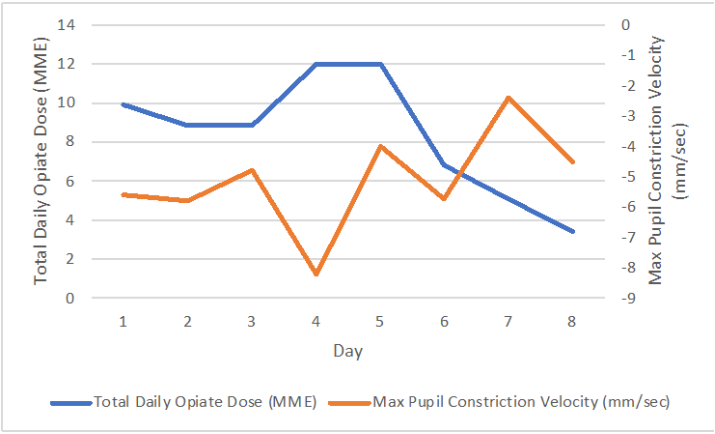

Figure 31. Total Daily Opiate Dose and Max Pupil Constriction Velocity
r_s = -0.37352, p (2-tailed) = 0.36206.

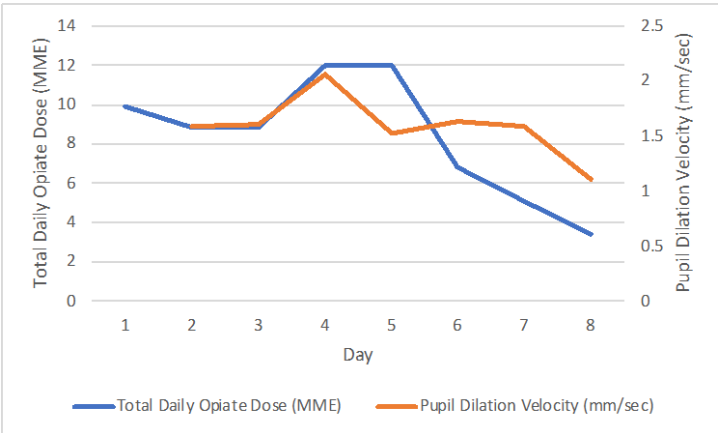

Figure 32. Total Daily Opiate Dose and Pupil Dilation Velocity
r_s = 0.1394, p (2-tailed) = 0.742.

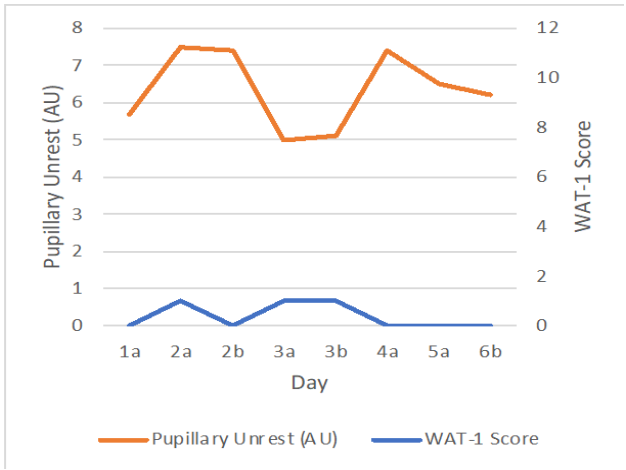

Figure 33. WAT-1 Score and Pupillary Unrest
r_s = -0.28341, p (2-tailed) = 0.49638.

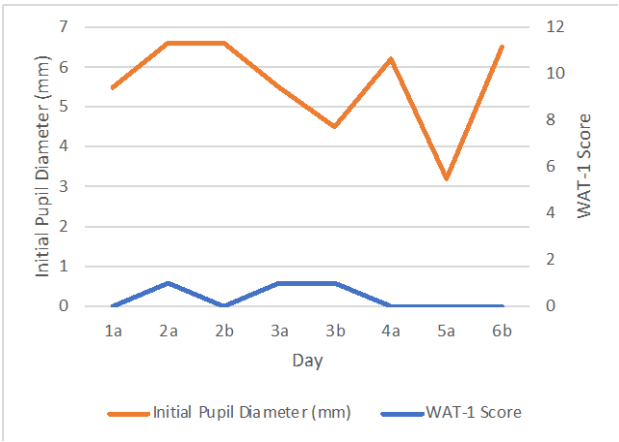

Figure 34. WAT-1 Score and Initial Pupil Diameter
r_s = -0.05703, p (2-tailed) = 0.89331.

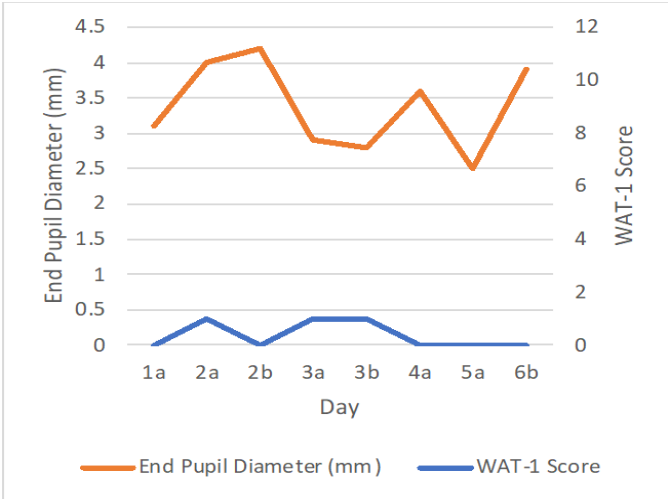

Figure 35. WAT-1 Score and End Pupil Diameter
r_s = -0.16903, p (2-tailed) = 0.68905.

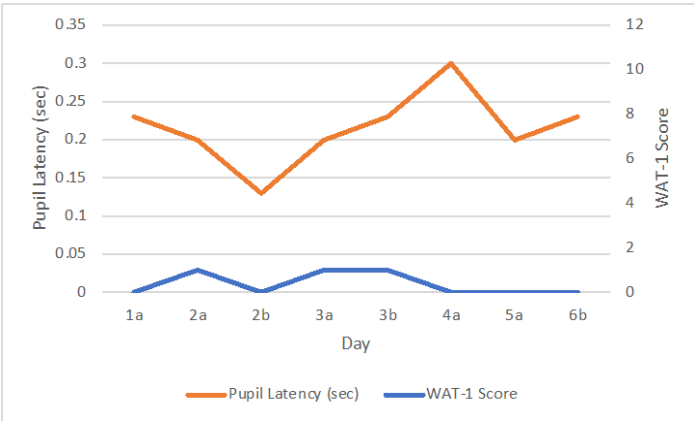

Figure 36. WAT-1 Score and Pupil Latency
r_s = -0.1777, p (2-tailed) = 0.67375.

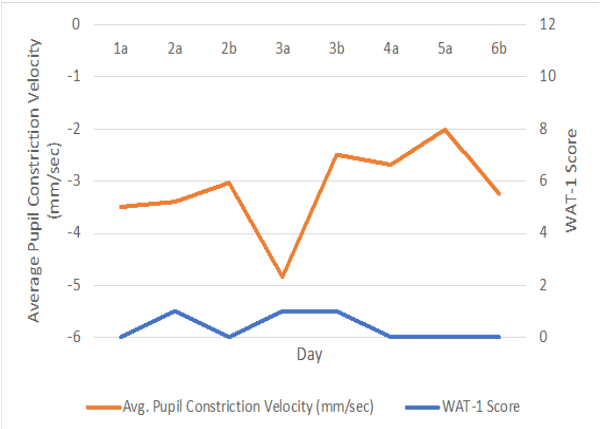

Figure 37. WAT-1 Score and Average Pupil Constriction Velocity
r_s = -0.28172, p (2-tailed) = 0.49906.

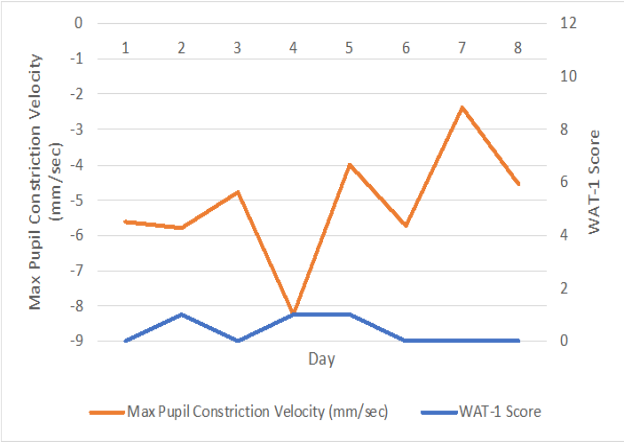

Figure 38. WAT-1 Score and Max Pupil Constriction Velocity
r_s = -0.3944, p (2-tailed) = 0.3336.

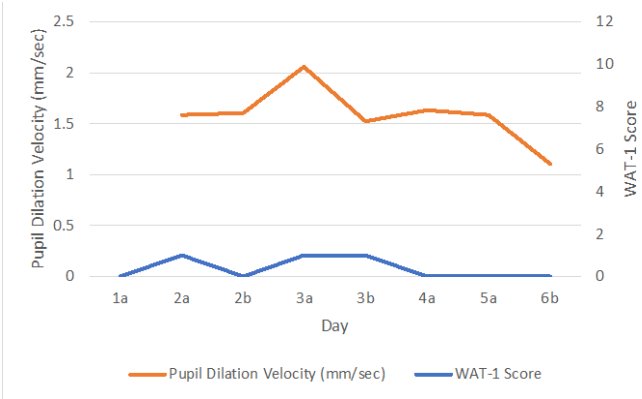

Figure 39. WAT-1 Score and Pupil Dilation Velocity
r_s = 0.22673, p (2-tailed) = 0.58923.

Subject 5:

Subject 5 was a Caucasian male infant admitted to the PICU for a submersion injury. He was enrolled on the study for a total of three days, with four data collection sessions (Table 5). Of note, day "2b" was a missed session. Total daily opiate dose ranged from 0.36 – 1.2 morphine milligram equivalents. WAT-1 score ranged from 0-1. Pupillary unrest was only able to calculate once and was therefore not included in statistical analysis. Initial pupil diameter ranged from 2.5-4.4mm. End pupil diameter ranged from 0.5-6.9mm. Pupil latency ranged from 0.13-0.47seconds. Average pupil constriction velocity ranged from -1.32 to -19.41mm/sec. Max pupil constriction velocity ranged from -3.11 to -43.84mm/sec. Pupil dilation velocity ranged from 5.26 to 14.17mm/sec, but the device was only able to capture the dilation velocity twice, and therefore, this value was not included in statistical analysis. The device was only able to calculate the time to reach 75% once, and therefore this value was not included in statistical analysis.

Each automated pupillometry value was compared to total daily opiate dose and to WAT-1 score. In addition, WAT-1 score was compared to total daily opiate dose. Spearman's rho was calculated for each comparison to determine if a statistically significant correlation between the values existed. For subject 5, there were no statistically significant correlations between pupillometry values, WAT-1 scores, and total daily opiate dose.

Table 5. Total Daily Opiate Dose, WAT-1 score, and Automated Pupillometry for Subject 5.

Day*	Total Daily Opiate Dose (MME)	WAT-1 Score	Pupillary Unrest (AU)	Initial Pupil Diameter (mm)	End Pupil Diameter (mm)	Pupil Latency (sec)	Average Pupil Constriction Velocity (mm/sec)	Max Pupil Constriction Velocity (mm/sec)	Pupil Dilation Velocity (mm/sec)	Time to reach 75% (sec)
1b	1.2	1	n/a	2.5	6.9	0.13	-1.78	-8.39	5.26	0.67
2a	0.76	0	2.8	2.9	1.6	0.27	-1.32	-3.11	n/a	n/a
2b	0.76	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
3a	0.36	0	n/a	3.4	1.8	0.3	-1.44	-3.15	n/a	n/a
3b	0.36	0	n/a	4.4	0.5	0.47	-19.41	-43.84	14.17	n/a

*Day noted as "a" or "b" to delineate morning (a) versus afternoon (b) data collection.

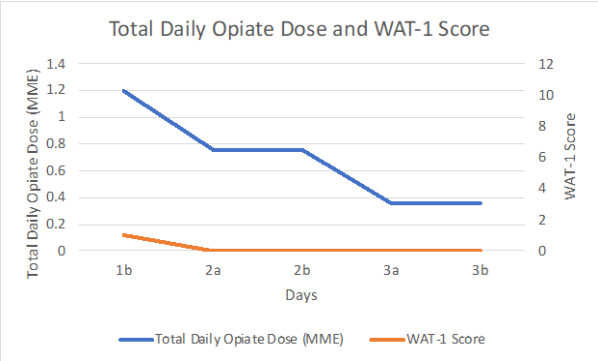

Figure 40. Total Daily Opiate Dose and WAT-1 Score
r_s = 0.74536, p (2-tailed) = 0.14822.

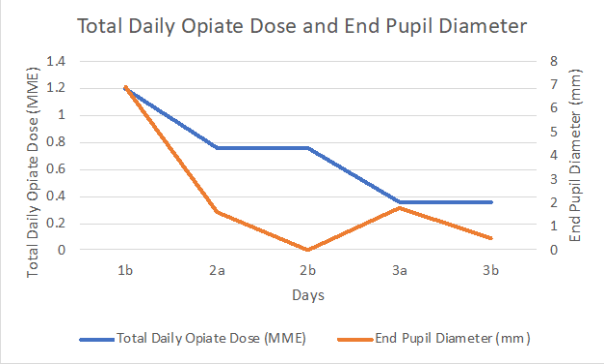

Figure 42. Total Daily Opiate Dose and End Pupil Diameter
r_s = 0.31623, p (2-tailed) = 0.60418.

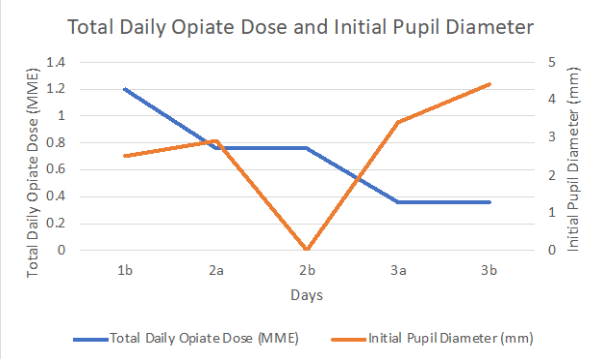

Figure 41. Total Daily Opiate Dose and Initial Pupil Diameter
r_s = -0.79057, p (2-tailed) = 0.11137.

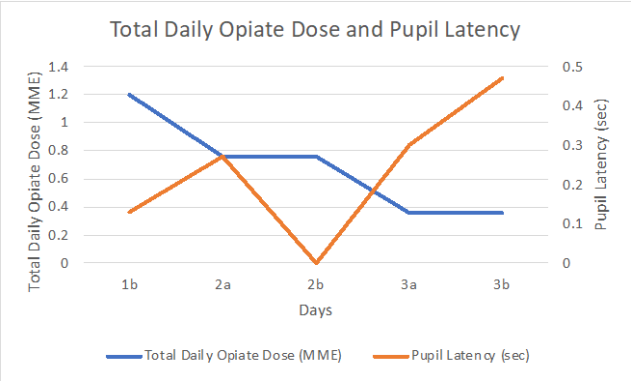

Figure 43. Total Daily Opiate Dose and Pupil Latency
r_s = -0.79057, p (2-tailed) = 0.11137.

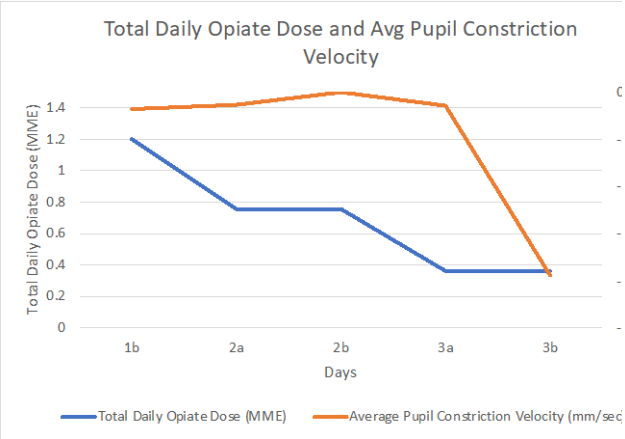

Figure 44. Total Daily Opiate Dose and Average Pupil Constriction Velocity
r_s = 0.26352, p (2-tailed) = 0.6684.

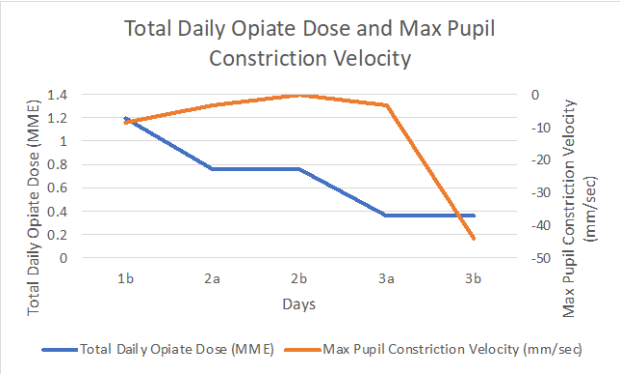

Figure 45. Total Daily Opiate Dose and Max Pupil Constriction Velocity
r_s = 0.26352, p (2-tailed) = 0.6684.

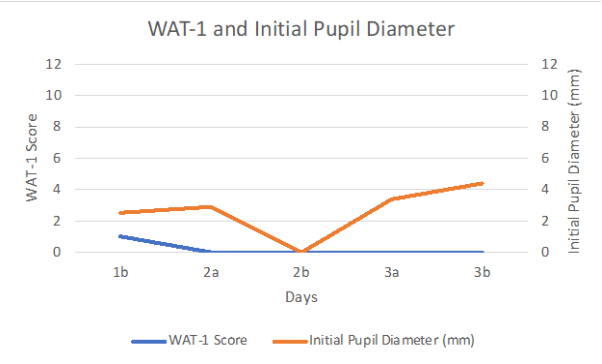

Figure 46. WAT-1 Score and Initial Pupil Diameter
r_s = -0.7746, p (2-tailed) = 0.2254.

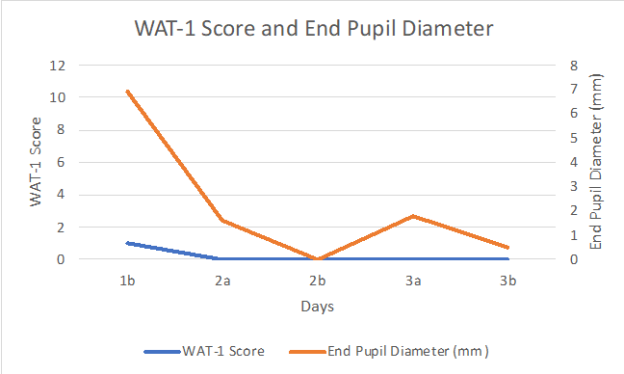

Figure 47. WAT-1 Score and End Pupil Diameter
r_s = 0.7746, p (2-tailed) = 0.2254.

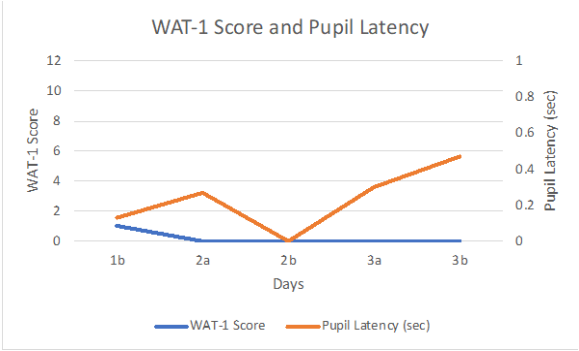

Figure 48. WAT-1 Score and Pupil Latency
r_s = -0.7746, p (2-tailed) = 0.2254.

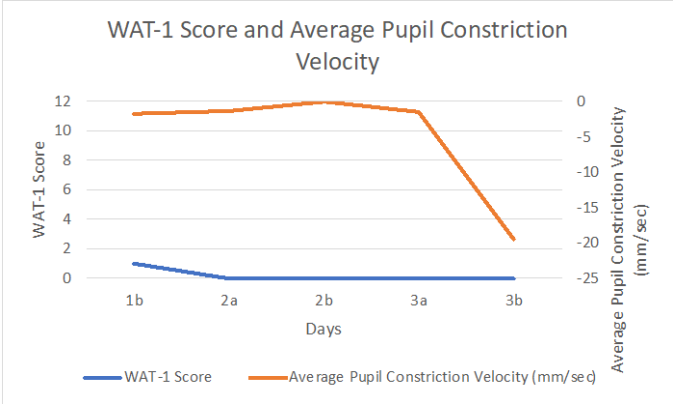

Figure 49. WAT-1 Score and Average Pupil Constriction Velocity
r_s = -0.2582, p (2-tailed) = 0.7418.

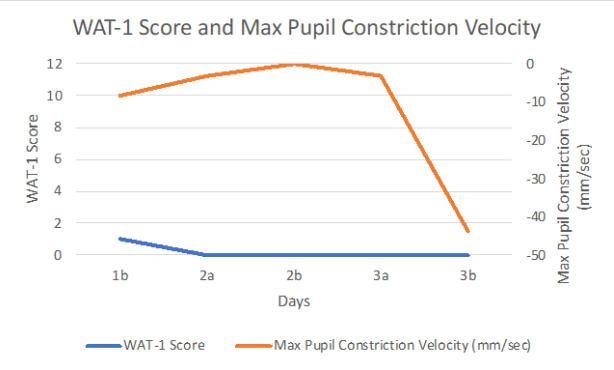

Figure 50. WAT-1 Score and Max Pupil Constriction Velocity

r_s = -0.2582, p (2-tailed) = 0.7418.

Discussion

There are currently no objective tools to evaluate for opiate abstinence syndrome in pediatric critical care patients tapering off opiates. Rather, clinicians rely on subjective measures, such as the Withdrawal Assessment Tool (WAT-1) to assess for signs or symptoms of opiate abstinence syndrome.

Automated pupillometry has been used in the adult population to monitor neurological complications and opiate tolerance (18,29). In children, automated pupillometry has been used to assess pain and increased intracranial pressure, with the NeurOptics NPi-200 device (19,20). To our knowledge, this is the first study to investigate the use of automated pupillometry to evaluate for opiate abstinence syndrome in children.

The data of the current exploratory study showed some statistically significant correlations between automated pupillometry and total daily opiate dose. Specifically, there was a statistically significant correlation between total daily opiate dose and initial pupil diameter and between total daily opiate dose and maximum constriction velocity in Subject 2. There was also a statistically significant correlation between total daily opiate dose and pupillary unrest in Subject 4 if assuming the last two time periods are outliers. There were no statistically significant correlations between total daily opiate dose and WAT-1 scores, and therefore, we have shown there is promising evidence that automated pupillometry is more sensitive to detecting opiate abstinence syndrome than the WAT-1 scoring system.

It is also important to note that the automated pupillometry data point "time to reach 75%" was unable to be calculated more than 50% of the time in all subjects. This variable was therefore unusable in data analysis and not a useful predictor of opiate abstinence syndrome.

However, there were several limitations to the current study. Small sample size and difficulties encountered while using the handheld automated pupillometry device may explain the statistically insignificant findings. For example, in Subject 1, the device was unable to detect the pupil in almost 40% of the pupillary light reflex data. This subject was an infant with dark irises. It is hypothesized that either the size of the pupil and/or the color of the iris contributed to the device's difficulty with identifying and calculating the pupillary changes.

Further, collecting automated pupillometry data on subjects who were tapering off sedation posed additional challenges. For example, Subject 2 became combative as he became less sedated. This agitation was amplified by the light stimulus from the automated pupillometry device, and it was difficult to collect the data for the 3-5 second duration that was required for the device to produce an accurate calculation.

Lastly, challenges arose with the feasibility of collecting data twice daily for the entire duration of the subject's hospitalization. For example, Subject 3 was enrolled on the study for 36 days. It would therefore be expected that this subject would have 72 total sessions where data was collected. However, there were only 45 total sessions with data collection. This was due to scheduling conflicts between the two investigators on study. Future studies may consider adding

more research personnel to the study to allow for more consistent data collection or decreasing data collection to once daily rather than twice daily.

Future Directions

When plotting the total daily opiate dose against pupillary unrest for Subject 4, it was noted that the values mirrored one another until the last two time points (Figure 26). Correlation between these time points was statistically significant (r_s= -0.85, p=0.03). However, when analyzing these values for the total duration on study, the correlation was not significant (r_s= -0.55, p=0.16). Even so, this perfectly opposing graph reveals a potential correlation between pupillary unrest and total daily opiate dose that should be investigated further.

Pupillary unrest is collected with the PLR-3000 by simply recording the pupil for five seconds without a light stimulus. The PLR-3000 then displays a value for pupillary unrest using arbitrary units in addition to a video of the pupil's movement and a graph showing pupil diameter (y-axis) against time (x-axis). Future studies may consider only investigating this value as it does not require a light stimulus and therefore may eliminate the challenges encountered with patients who were agitated at baseline. In addition, pupillary unrest was successfully collected in Subject 1, even though there were difficulties collecting the pupillary light reflex values in this patient. Therefore, pupillary unrest may not require a standardized pupil size or iris color.

Lastly, ultrasound has been shown to monitor pupillary changes during general anesthesia (36). Future studies could therefore utilize this non-invasive method to measure pupillary changes if the automated pupillometry device becomes overly bothersome to the pediatric patient who is tapering off opiates and sedation.

Conclusions

This study investigated whether automated pupillometry was an objective assessment of opiate abstinence syndrome in pediatric critical care patients who are tapering off opiates, when compared to the more subjective Withdrawal Assessment Tool-1. Results revealed significant correlation between automated pupillometry and total daily opiate dose, but not between between automated pupillometry and WAT-1 scores. Therefore, this study showed automated pupillometry may be more sensitive in detecting opiate abstinence syndrome when compared to the WAT-1 scoring system.

Future studies may consider investigating pupillary unrest further as it shows potential to correlate with total daily opiate dose. Additionally, ultrasound may be a more effective method to measure pupillary changes in pediatric patients as it is also a non-invasive device, and it does not emit a light stimulus.

Compliance

This research project obtained IRB approval through Cook Children's Health Care System and maintained annual review requirements throughout the duration of the project. The investigators completed and maintained CITI training for participation in human subject research.

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