Received: 22 April 2022 | Revised: 24 August 2022 | Accepted: 2 September 2022

DOI: 10.1002/emp2.12825

JACEP OPEN
JOURNAL OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS OPEN
A GLOBAL JOURNAL OF EMERGENCY MEDICINE
WILEY

BRIEF RESEARCH REPORT

Toxicology

Impact of acute intoxication on quantitative pupillometry assessment in the emergency department

Eliana L. Jolkovsky BA[1,*] | **Felix E. Fernandez-Penny BS**[2,3,*] | **Maya Alexis BS**[2] | **Lauren N. Benson BA**[2] | **Bo Hwan Wang BS**[2] | **Benjamin S. Abella MD, MPhil**[2,3]

[1]David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA

[2]Department of Emergency Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[3]Penn Acute Research Collaboration, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence
Benjamin S. Abella, MD, MPhil, Department of Emergency Medicine, University of Pennsylvania, 3400 Spruce Street Ground Ravdin, Philadelphia, PA 19104, USA.
Email: Benjamin.abella@pennmedicine.upenn.edu

Funding and support: By *JACEP* Open policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

*These two authors contributed equally to the work.

Abstract

Study Hypothesis/Objective: This prospective cohort study aimed to assess whether and to what extent different quantitative pupillometry (QP) metrics are associated with different intoxicant drug classes as well as investigate the potential benefit of QP as a tool in the rapid assessment of clinically intoxicated patients in the emergency department (ED).

Methods: Between February 25, 2019 and April 24, 2021, 325 patients were enrolled in the EDs of the Hospital of the University of Pennsylvania (HUP) and Penn Presbyterian Medical Center (PPMC). Patients deemed clinically intoxicated or in withdrawal by an attending emergency physician were considered for eligibility. Patients <18 years old, with a chief complaint indicative of head trauma or stroke or without a urine drug screen (UDS) positive for drugs of abuse were excluded. QP data were also collected from a cohort of 82 healthy control subjects.

Results: Neurological Pupil index (NPi) values did not vary significantly between control and study groups nor between study group patients with a UDS positive for opioids. With exception of latency of constriction, all other QP metrics for the study group were depressed relative to controls ($P < 0.005$).

Conclusions: This work demonstrated the feasibility of QP measurement in the ED, finding that NPi remains unaffected by clinical intoxication and therefore can potentially be used for ED patient evaluation without risk of confounding by key intoxicants of abuse. Future work will evaluate the value of QP as a means of rapid and reproducible neurological assessment to identify various pathologies.

KEYWORDS
emergency medicine, intoxication, opioid use, pupillometry, substance use

Supervising Editor: Karl Sporer, MD.

1 | INTRODUCTION

1.1 | Background and importance

Alcohol and other substance intoxication accounts for more than 4 million emergency department visits annually[1–3] and thus represents a major diagnostic and treatment burden in emergency medicine practice. With an average 95,000 alcohol-related fatalities annually[4] and nearly 80% of the 100,000+ drug overdose deaths involving opioids in 2021 alone,[5] emergency medical services (EMS) agencies and EDs face challenges associated with the rapid assessment, treatment, and monitoring for intoxication. Furthermore, the evaluation of causes of mental status changes because of stroke, infection, or metabolic derangements may be confounded by coincident intoxication.

Quantitative pupillometry (QP) represents the automated, electronic measurement of pupillary size and light reactivity, including variables such as constriction velocity, latency, and more. The well-known association of pupillary response with neurologic pathways has supported the use of QP as a routinely employed and effective measure in the assessment and prediction of outcomes for patients with diverse pathologies spanning traumatic brain injury and other neurological issues.[6–10]

Already widely in use in critical care settings and with documented applications in the detection of neurological injuries and determination of efficacy of different interventions, QP may present value to emergency clinicians as a non-invasive, rapid, and precise diagnostic approach for use in the detection and treatment of intoxicated patients. Whether QP can be used to assess patients for intoxication or from ethanol or key drugs of abuse, and whether QP measurements of mental status change would be made unreliable because of intoxicated states, remains unknown.

1.2 | Goals of this investigation

This prospective cohort feasibility study aimed to assess whether and to what extent different QP metrics are associated with different intoxicant drug classes as well as provide insight into potential benefits of QP as a tool in the rapid assessment of ED patients.

2 | METHODS

2.1 | Study design and setting

Between February 25, 2019 and April 24, 2021, patients were prospectively enrolled in the EDs of the Hospital of the University of Pennsylvania (HUP) and Penn Presbyterian Medical Center (PPMC), both tertiary academic hospitals in Philadelphia. University of Pennsylvania Institutional Review Board approval was granted to conduct this study.

The Bottom Line

Quantitative pupillometry (QP) is a method to measure pupillary size and reactivity. QP was measured in 325 patients with suspected drug intoxication. No statistical differences in the Neurological Pupil Index were noted between those with intoxication versus control patients. This study demonstrated feasibility of using QP in the emergency department.

2.2 | Selection of participants

Adult patients deemed clinically intoxicated or in withdrawal, as reflected in the electronic health record and with a urine drug screen (UDS) positive for ethanol, opioids, or other key drugs of abuse were considered for eligibility. Inclusion criteria were verified by chart review before analysis. Exclusion criteria included (1) age <18 years or (2) a chief complaint indicative of head trauma or stroke, to avoid possible confounders that might affect QP measurement owing to intoxicants. QP data also were collected from a cohort of healthy control subjects selected among credentialed ED staff including residents, medical students, attending physicians, and research personnel.

2.3 | Measurements

Upon subject identification, QP data were collected by trained research assistants using the NeurOptics NPi-200 Pupillometer (NeurOptics, Inc., Irvine, CA, USA) according to standard operating procedures. The NeurOptics NPi-200 pupillometer (NeurOptics, Irvine, CA, USA) is a Food and Drug Administration-approved, hand-held, infrared, photographic device that enables measurement of QP metrics. The device is positioned at a consistent distance from the subject, after which a beam of light is administered over a 3-second interval during which images of the pupil are captured at a rate of more than 30 frames per second and subsequently analyzed. The device has been well evaluated for the replicability, precision, and accuracy of its measurements in various settings.[11–15]

Collected metrics included (1) maximum pupil diameter ($Size_{max}$), (2) minimum pupil diameter ($Size_{min}$), (3) constriction % or percentage change (CH %), (4) constriction velocity, (5) maximum constriction velocity, (6) latency of constriction (LAT), (7) dilation velocity, and (8) the Neurological Pupil index (NPi)—a composite metric taking into account the other 7 measurements. QP measurements are compared against a reference set from healthy individuals and used to generate Z-scores that are ultimately combined to generate the NPi value, using a proprietary algorithm. The NPi ranks pupil reactivity on a scale from 0 to 5, with a 0 value representing a non-reactive, immeasurable, or other atypical response. Values less than 3.0 have been validated as abnormal or "sluggish;" whereas, those above are considered normal.[16]

UDS data collected as part of clinical care were abstracted from the emergency medical record for patients deemed clinically intoxicated by ED physicians. Clinically intoxicated patients were designated either opioid positive or opioid negative on the basis of UDS results. The screening assay used incorporates a Beckman platform immunoassay with positive results reflexed for further confirmation by mass spectrometry. The screening includes tests for amphetamines, barbiturates, benzodiazapines, cocaine metabolites, ethanol, methadone, opiates (including oxycodone and fentanyl), phencyclidine, and tetrahydrocannibinol (THC).

All data were stored in an electronic, Health Insurance Portability and Accountability Act-compliant clinical database (REDCap, Vanderbilt University) and reviewed monthly by study coordinators for quality assurance purposes.

2.4 | Analysis

Left and right eye QP metrics were averaged for analysis. Differences in QP measures between clinically intoxicated subjects and the control group as well as differences between opioid +/- groups were assessed using 1-tailed *t* tests.

3 | RESULTS

3.1 | Characteristics of study subjects

A total of 325 patients were enrolled during the recruitment period. Patients were excluded if lacking a UDS to provide biochemical confirmation of specific intoxicants or subsequently deemed not intoxicated (n = 174). Those with incomplete measurements (ie, data collected from only 1 eye or interruptions affecting data quality) were also removed from consideration (n = 32). This yielded a final data set of 119 patients. QP data were also collected from a cohort of 82 healthy control subjects.

The study cohort had a median age of 38 years (Q1 = 28; Q3 = 50.5) and was 34% female. A total of 55% presented with single substance intoxication and 45% with polysubstance intoxication. Ethanol intoxication was present in 82% of the study population; opioids, THC, and cocaine were the next most prevalent intoxicants (29%, 25%, and 23%, respectively). The control group had a median age of 28 years (Q1 = 25; Q3 = 33) and was 66% female. Control group subjects, all ED staff, were healthy, alert, and oriented and self-reported lack of intoxicant use, in accordance with standing hospital policies (Table 1).

TABLE 1 Study population and control group select demographics and UDS correlates

Item	Patients (n, %)	Controls (n, %)
Gender		
Female	41 (34)	54 (66)
Age, y		
18–35	53 (45)	65 (79)
36–50	35 (29)	14 (17)
50+	31 (26)	3 (4)
Intoxication status		
Single substance intoxication	66 (55)	
Polysubstance intoxication	53 (45)	
Lab confirmed intoxicants		
Opioids	35 (29)	
Cocaine metabolites	28 (24)	
Barbiturates	5 (4)	
Benzodiazapines	25 (21)	
Phencyclidine	12 (10)	
Tetrahydrocannibinol	30 (25)	
Amphetamines	7 (6)	
Ethanol	98 (82)	

Abbreviation: UDS, urine drug screen

3.2 | Main results

Relative to the control group (without intoxication), individual QP metrics for the study group of clinically intoxicated patients confirmed by UDS findings varied significantly ($P < 0.005$) for all 7 metrics. With exception of LAT, all measures were depressed in the study group relative to the controls. However, the composite NPi values did not vary significantly between control and study groups (4.31 ± 0.32 vs 4.29 ± 0.49, $P = 0.81$), suggesting that NPi values remain independent of intoxication status (Table 2).

When specifically evaluated in the context of opioid intoxication, no significant difference in QP metrics, including NPi, was found between patients with or without a UDS positive for opioids (Table 3). For example, the composite NPi values were statistically indistinguishable (4.22 ± 0.52 vs 4.32 ± 0.48, $P = 0.31$).

4 | LIMITATIONS

As a feasibility study of ED-based QP, this work may be underpowered and warrants additional investigation to confirm associations and trends between QP measures, intoxication severity, and specific intoxicants. Polysubstance intoxication in a substantial fraction of the study cohort may also have introduced confounding variables into the analysis. Patients were enrolled and QP data collected only over the course of their ED stay and; therefore, we did not obtain subsequent QP measurements of non-intoxicated "baseline" state as internal controls. Given feasibility issues and that this study made use of laboratory tests ordered as part of clinical care as opposed to research-specific testing, control subjects were not subject to UDS testing that patient

TABLE 2 Differences in mean quantitative pupillometry metrics (Control vs clinically intoxicated)

Pupillary measurement	Abbreviation	Mean Values ± SD		*P* value (*t* test)
		Controls [n = 82]	Clinically intoxicated with UDS correlate [n = 119]	
Neurological Pupil Index	NPI	4.31 ± 0.32	4.29 ± 0.49	0.81
Max diameter (mm)	SizeMax	4.33 ± 0.76	3.55 ± 1.20	<0.05
Min diameter (mm)	SizeMin	2.85 ± 0.45	2.51 ± 0.69	<0.05
Percentage of change	CH%	33.80 ± 5.86	27.15 ± 10.02	<0.05
Constriction velocity (mm/sec)	CV	2.75 ± 0.78	1.99 ± 1.17	<0.05
Max constriction velocity (mm/sec)	MCV	4.11 ± 1.05	2.97 ± 1.46	<0.05
Latency of constriction (sec)	LAT	0.23 ± 0.02	0.26 ± 0.07	<0.05
Dilation velocity (mm/sec)	DV	1.13 ± 0.33	0.88 ± 0.43	<0.05

Abbreviation: UDS, urine drug screen

TABLE 3 Differences in mean quantitative pupillometry metrics by presence/absence of opioids

Pupillary measurement	Abbreviation	Mean Values ± SD		*P* value (*t* test)
		Positive for opioids only [n = 35]	Negative for opioids [n = 84]	
Neurological Pupil Index	NPI	4.22 ± 0.52	4.32 ± 0.48	0.31
Max diameter (mm)	SizeMax	3.38 ± 1.18	3.62 ± 1.20	0.33
Min diameter (mm)	SizeMin	2.46 ± 0.68	2.53 ± 0.69	0.61
Percentage of change	CH%	24.56 ± 8.40	28.23 ± 10.47	0.07
Constriction velocity (mm/sec)	CV	1.74 ± 0.91	2.09 ± 1.26	0.14
Max constriction velocity (mm/sec)	MCV	2.70 ± 1.40	3.08 ± 1.48	0.20
Latency of constriction (sec)	LAT	0.25 ± 0.04	0.26 ± 0.08	0.46
Dilation velocity (mm/sec)	DV	0.80 ± 0.46	0.91 ± 0.41	0.24

subjects received. Lack of intoxicant usage among control subjects was self-reported and may underrepresent prevalence.

5 | DISCUSSION

Our prospective evaluation of QP metrics in intoxicated adult patients found (1) that Neurological Pupil Index is independent of intoxicants, and (2) that QP can be used in the evaluation of patients in the ED without risk of confounding by intoxicants such as opioids. This finding supports the notion that QP may play a role in the assessment of ED patients with neurologic complaints, the subject of future work, with the knowledge that confounding from intoxicants may be minimal.

Although clinical intoxication did affect pupil size and other individual metrics of dynamic pupillary function, our study found that intoxicants did not alter the composite metric, the NPi. A sensitivity analysis was performed excluding measurements collected from patients with positive UDS screens but exhibiting withdrawal symptoms, which similarly did not show a significant difference in mean NPi values (data not shown). These findings suggest that NPi may be a useful indicator of neurologic function irrespective of intoxicated states including those attributed to opioids. Future work will be required to assess the potential role of QP for rapid and standardized assessment of patients with potential cerebrovascular accidents and other neurologic causes of mental status changes.

Other work has examined applications for QP in various clinical settings and suggested its value in the critical care neurological assessment of patients with known stroke, cardiac arrest, and traumatic brain injury.[17–19] Our findings are consistent with recent work demonstrating that NPi remained unchanged in the presence of varying levels of remifentanil.[20] In our cohort, which included patients with intoxication from an undifferentiated range of synthetic and natural opioids, we similarly observed an insignificant effect on NPi values. To our knowledge, this study represents the first evaluation of the use of QP in a cohort of clinically intoxicated ED patients.

NPi represents a summary metric, built on an algorithm synthesizing other component measurements of pupillary function. Thus, NPi provides a single standardized metric that may inform a comprehensive assessment of pupillary, and correspondingly neurological, function and response. Although significant differences in NPi and other QP

metrics have been identified among neurocritical care patients of different age groups and gender,[21] we are not aware of studies indicating differences for different demographic groups in good health. The lack of association between NPi and intoxication state suggests that although it cannot act as a substitute for standard laboratory toxicology testing, intoxicants are unlikely to cloud a neurological assessment by QP. Depressed values for other QP measures in study patients relative to controls suggest that serial measurements may be useful in monitoring mental status changes and/or in the initial assessment of intoxicated patients in the ED or prehospital emergency care.

ED-based assessment of patients with altered mental status is limited in current practice by the use of subjective evaluation coupled with the variable availability and time associated with serum and laboratory testing. Qualitative assessment of pupils with hand-held light sources are subject to variable interpretation by assessors.[22] This also hinders the comparison of multiple measurements over time. Therefore, QP may fill an unmet need, if future work confirms its utility as an early diagnostic tool for other pathologies unrelated to alcohol or other substance use. Quantitative measures may also provide added value in terms of data standardization and reduce variability in interpretation across medical teams and shift changes during longitudinal care of patients with brain injuries, as shown in prior work.[11–15]

Our work has demonstrated the feasibility of QP measurement in the ED setting. Our key finding, that NPi remains unaffected by intoxication, raises the possibility of future work to evaluate the value of QP as a means of rapid and reproducible neurological assessment to identify various pathologies (eg, traumatic brain injury or cerebrovascular accident). Further research will be required to identify precise use cases and associations between NPi and specific diagnoses.

AUTHOR CONTRIBUTIONS

Eliana L. Jolkovsky and Benjamin S. Abella conceived and designed the study; Benjamin S. Abella acquired research funding and provided project oversight. Eliana L. Jolkovsky and Felix E. Fernandez-Penny oversaw the data collection team, maintained quality assurance measures throughout the study period, ran preliminary analyses, and informed manuscript drafting. Felix E. Fernandez-Penny supported data collection and organization, led manuscript drafting and development, and provided project team oversight. Maya Alexis completed statistical analysis and table/figure preparation and contributed to manuscript revision. Bo Hwan Wang and Lauren N. Benson contributed to data collection, scoring, and analysis.

ACKNOWLEDGMENTS

The authors thank the University of Pennsylvania Emergency Medicine Academic Associates Program, whose members were responsible for point-of-care pupillometry data collection. This work was supported by funding from NeurOptics Inc., Irvine, CA.

CONFLICTS OF INTEREST

Dr. Abella is a consultant for Becton Dickinson, Stryker, NeurOptics, and Zoll. He holds equity in VOC Health and MDAlly.

REFERENCES

1. Albert M, McCaig LF, Uddin S. NCHS Data Brief No. 196; Emergency department visits for drug poisoning: United States, 2008–2011. Centers for Disease Control and Prevention. Published April 2015. Accessed November 2021. https://www.cdc.gov/nchs/products/databriefs/db196.htm
2. Mullins PM, Mazer-Amirshahi M, Pines JM. Alcohol-related visits to US emergency departments, 2001–2011. *Alcohol Alcohol*. 2017;52(1):119-125. https://doi.org/10.1093/alcalc/agw074
3. National Hospital Ambulatory Medical Care Survey: 2018 emergency department summary tables. CDC – National Center for Health Statistics. Published October 1, 2021. Accessed November 2021. https://www.cdc.gov/nchs/ahcd/web_tables.htm
4. Alcohol facts and statistics. National Institute on Alcohol Abuse and Alcoholism (NIAAA) (NIH). Published June 2021. Accessed November 2021. https://www.niaaa.nih.gov/publications/brochuresand-fact-sheets/alcohol-facts-and-statistics
5. U. S. Overdose deaths in 2021 increased half as much as in 2020 - but are still up 15%. Centers for Disease Control and Prevention. Published May 11, 2022. Accessed August, 2022. https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/202205.htm
6. Romagnosi F, Bernini A, Bongiovanni F, et al. Neurological pupil index for the early prediction of outcome in severe acute brain injury patients. *Brain Sci*. 2022;12(5):609. https://doi.org/10.3390/brainsci12050609
7. Jahns FP, Miroz JP, Messerer M, et al. Quantitative pupillometry for the monitoring of intracranial hypertension in patients with severe traumatic brain injury. *Crit Care*. 2019;23(1):155. https://doi.org/10.1186/s13054-019-2436-3
8. Privitera CM, Neerukonda SV, Aiyagari V, et al. A differential of the left eye and right eye neurological pupil index is associated with discharge modified Rankin scores in neurologically injured patients. *BMC Neurol*. 2022;22(1):273. https://doi.org/10.1186/s12883-022-02801-3
9. Zafar SF, Suarez JI. Automated pupillometer for monitoring the critically ill patient: a critical appraisal. *J Crit Care*. 2014;29(4):599-603. https://doi.org/10.1016/j.jcrc.2014.01.012
10. Lee MH, Mitra B, Pui JK, Fitzgerald M. The use and uptake of pupillometers in the Intensive Care Unit. *Aust Crit Care*. 2018;31(4):199-203. https://doi.org/10.1016/j.aucc.2017.06.003
11. Du R, Meeker M, Bacchetti P, Larson MD, Holland MC, Manley GT. Evaluation of the portable infrared pupillometer. *Neurosurgery*. 2005;57(1):198-203; discussion 198–203. https://doi.org/10.1227/01.neu.0000163425.79170.cb
12. Meeker M, Du R, Bacchetti P, et al. Pupil examination: validity and clinical utility of an automated pupillometer. *J Neurosci Nurs*. 2005;37(1):34-40.
13. Schallenberg M, Bangre V, Steuhl KP, Kremmer S, Selbach JM. Comparison of the Colvard, Procyon, and Neuroptics pupillometers for measuring pupil diameter under low ambient illumination. *J Refract Surg*. 2010;26(2):134-143. https://doi.org/10.3928/1081597X-20100121-09
14. Zhao W, Stutzman S, DaiWai O, Saju C, Wilson M, Aiyagari V. Inter-device reliability of the NPi-100 pupillometer. *J Clin Neurosci*. 2016;33:79-82. https://doi.org/10.1016/j.jocn.2016.01.039
15. Stutzman S, Iype P, Marshall J, et al. Inter-device reliability of the NPi-200 and NPi-300 pupillometers. *J Clin Neurosci*. 2022;100:180-183. https://doi.org/10.1016/j.jocn.2022.04.023
16. Chen JW, Gombart ZJ, Rogers S, Gardiner SK, Cecil S, Bullock RM. Pupillary reactivity as an early indicator of increased intracranial pressure: the introduction of the Neurological Pupil index. *Surg Neurol Int*. 2011;2:82. https://doi.org/10.4103/2152-7806.82248
17. Traylor JI, El Ahmadieh TY, Bedros NM, et al. Quantitative pupillometry in patients with traumatic brain injury and loss of consciousness: a prospective pilot study. *J Clin Neurosci*. 2021;91:88-92. https://doi.org/10.1016/j.jocn.2021.06.044

18. Marshall M, Deo R, Childs C, Ali A. Feasibility and variability of automated pupillometry among stroke patients and healthy participants: potential implications for clinical practice. *J Neurosci Nurs*. 2019;51(2):84-88. https://doi.org/10.1097/JNN.0000000000000416
19. Riker RR, Sawyer ME, Fischman VG, et al. Neurological pupil index and pupillary light reflex by pupillometry predict outcome early after cardiac arrest. *Neurocrit Care*. 2020;32(1):152-161. https://doi.org/10.1007/s12028-019-00717-4
20. McKay RE, Larson MD. Detection of opioid effect with pupillometry. *Auton Neurosci*. 2021;235:102869. https://doi.org/10.1016/j.autneu.2021.102869
21. Lussier BL, Stutzman SE, Atem F, et al. Distributions and reference ranges for automated pupillometer values in neurocritical care patients. *J Neurosci Nurs*. 2019;51(6):335-340. https://doi.org/10.1097/JNN.0000000000000478
22. Olson DM, Stutzman S, Saju C, Wilson M, Zhao W, Aiyagari V. Interrater reliability of pupillary assessments. *Neurocrit Care*. 2016;24(2):251-257. https://doi.org/10.1007/s12028-015-0182-1

AUTHOR BIOGRAPHY

Eliana Jolkovsky, BA, is a medical student at David Geffen School of Medicine, University of California in Los Angeles, CA.

How to cite this article: Jolkovsky EL, Fernandez-Penny FE, Alexis M, Benson LN, Wang BH, Abella BS. Impact of acute intoxication on quantitative pupillometry assessment in the emergency department. *JACEP Open*. 2022;3:e12825. https://doi.org/10.1002/emp2.12825