No. 17-5198

IN THE

Supreme Court of the United States

GARY OTTE, RONALD PHILLIPS, AND RAYMOND TIBBETTS,

Petitioners,

v.

RONALD ERDOS, ET AL.,

Respondents.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Sixth Circuit

BRIEF OF FIFTEEN PROFESSORS OF PHARMACOLOGY AS *AMICI CURIAE* IN SUPPORT OF CERTIORARI

JOHN Q. LEWIS
Counsel of Record
JON W. OEBKER
JENNIFER L. MESKO
CHAD M. EGGSPUEHLER
AMANDA N. JOHNSON
TUCKER ELLIS LLP
950 Main Avenue, Ste. 1100
Cleveland, OH 44113
(216) 592-5000
john.lewis@tuckerellis.com

Counsel for Amici Curiae

July 24, 2017

WILSON-EPES PRINTING CO., INC. – (202) 789-0096 – WASHINGTON, D. C. 20002

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

CASES

OTHER AUTHORITIES

STATEMENT OF INTEREST OF AMICI CURIAE

Amici curiae, each of whom is listed below, are professors of pharmacology at universities in the United States.[1] As they did in *Glossip v. Gross*, 135 S. Ct. 2726 (2015), amici respectfully submit this brief to provide a pharmacological perspective on the physiologic effect of midazolam hydrochloride ("midazolam"). See Br. of Sixteen Professors of Pharmacology as Amici Curiae in Support of Neither Party, 2015 WL 1247193 (Mar. 18, 2015) (*Glossip* Amici).

Midazolam is a sedative in the benzodiazepine class of drugs that the State of Ohio decided to use as a substitute for barbiturates, like sodium thiopental and pentobarbital, as the first drug in the State's three-drug lethal injection protocol. Amici have no interest in any party to this litigation, nor any stake in the outcome of this case.[2]

---

[1] No counsel for a party authored any portion of this brief. No person other than the amici, or their counsel, made a monetary contribution to fund the preparation or submission of this brief. Letters from the parties consenting to the filing of this amicus curiae brief have been filed with the Clerk of the Court. At respondents' request, amici note that the filing of this brief occurred after respondents filed their brief in opposition, and so respondents did not have an opportunity to respond to this amicus brief.

[2] Each amicus curiae submits this brief in his or her individual capacity. All of the institutional,

Edward Bilsky, Ph.D. is a Professor of Pharmacology at the University of New England in Biddeford, ME. At the University of New England, Dr. Bilsky is also the Founding Director of the Center for Excellence in the Neurosciences. Dr. Bilsky received a Ph.D. in Pharmacology and Toxicology from the University of Arizona in Tucson, AZ. Dr. Bilsky was a Post-Doctoral Research Fellow in Neuroscience at the University of Arizona.

Kathryn A. Cunningham, Ph.D. is the Chauncey Leake Distinguished Professor of Pharmacology, Vice Chairman of the Department of Pharmacology and Toxicology, and the Director of the Center of Addiction Research at the University of Texas Medical Branch in Galveston, TX. Dr. Cunningham received a Ph.D. in Experimental Psychology (Behavioral Neuropharmacology) from the University of South Carolina in Columbia, SC. She completed a Post-Doctoral Fellowship in the Department of Pharmacology and Toxicology at the University of Texas Medical Branch in Galveston, TX.

Kenneth E. McCarson, Ph.D. is a Professor in the Department of Pharmacology, Toxicology, and Therapeutics at the University of Kansas Medical Center in Kansas City, KS. Dr. McCarson received a Ph.D. in Pharmacology, with distinction, from the Medical College of Georgia in Augusta, GA. Dr. McCarson was a Post-Doctoral Research Associate in Neurobiology at the

---

organizational, and professional affiliations noted in this section are for identification purposes only.

Washington University School of Medicine in St. Louis, MO.

Christopher R. McCurdy, Ph.D. is a Professor of Medicinal Chemistry and Director of the University of Florida Translational Drug Development Core at the University of Florida in Gainesville, FL. Dr. McCurdy received a Ph.D. in Medicinal Chemistry from the University of Georgia in Athens, GA. Dr. McCurdy completed a Post-Doctoral Research Fellowship in Medicinal Chemistry at the University of Minnesota in Minneapolis, MN.

Jay McLaughlin, Ph.D. is an Associate Professor of Pharmacodynamics at the University of Florida College of Pharmacy in Gainesville, FL. Dr. McLaughlin received a Ph.D. in Neuroscience from the University of Rochester, School of Medicine and Dentistry in Rochester, NY. Dr. McLaughlin completed Post-Doctoral Research Fellowships at the University of Rochester in Rochester, NY, and at the University of Washington in Seattle, WA.

S. Stevens Negus, Ph.D. is a Professor of Pharmacology in the Department of Pharmacology and Toxicology at Virginia Commonwealth University in Richmond, VA. Dr. Negus received a Ph.D. in Neurobiology from the University of North Carolina in Chapel Hill, NC. Dr. Negus completed a Post-Doctoral Fellowship at the Scripps Research Institute in La Jolla, CA, and served on faculties at the University of Michigan in Ann Arbor, MI, and Harvard Medical School in Boston, MA.

Dennis J. Paul, Ph.D. is a Professor of Pharmacology in the Department of Pharmacology and Experimental Therapeutics at the Louisiana State University School of Medicine in New Orleans, LA. Dr. Paul received a Ph.D. in Biopsychology from the University of British Columbia in Vancouver, BC. Dr. Paul was a Post-Doctoral Fellow in the Cotzias Laboratory for Neuro-Oncology at Memorial Sloan-Kettering Cancer Center in New York, NY.

Frank Porreca, Ph.D. is a Professor of Pharmacology and Anesthesiology at the University of Arizona College of Medicine in Tucson, AZ. Dr. Porreca received a Ph.D. in Pharmacology from Temple University in Philadelphia, PA. Dr. Porreca completed his post-doctoral research in the Department of Pharmacology at the University of Arizona in Tucson, AZ.

Amynah Pradhan, Ph. D. is an Assistant Professor of Pharmacology in the Department of Psychiatry at the University of Illinois at Chicago in Chicago, IL. Dr. Pradhan received a Ph.D. in Pharmacology from McGill University in Montréal, Québec, CA. Dr. Pradhan completed post-doctoral fellowships at the Institut de Génétique et de Biologie Moléculaire et Cellulaire in Strasbourg, France and the University of California Los Angeles.

Paul L. Prather, Ph.D. is a Professor of Pharmacology in the Department of Pharmacology and Toxicology at the University of Arkansas for Medical Sciences in Little Rock, AR. Dr. Prather

received a Ph.D. in Pharmacology from the University of Georgia College of Pharmacy in Athens, GA. Dr. Prather completed his post-doctoral research in the Department of Pharmacology at University of North Texas Health Science Center in Fort Worth, TX, and in the Department of Pharmacology at the University of Minnesota School of Medicine in Minneapolis, MN.

Sandra C. Roerig, Ph.D. is a Professor in the Department of Pharmacology, Toxicology and Neuroscience; Dean of Graduate Studies; and Associate Dean of Research at Louisiana State University Health Sciences Center in Shreveport, LA. Dr. Roerig received a Ph.D. in Pharmacology from the Medical College of Wisconsin in Milwaukee, WI. Dr. Roerig completed her post-doctoral research in the Department of Pharmacology at the University of Minnesota in Minneapolis, MN.

Kelly M. Standifer, Ph.D. is a Professor of Pharmacology and Chair of the Department of Pharmaceutical Sciences at the University of Oklahoma College of Pharmacy in Oklahoma City, OK. Dr. Standifer received a Ph.D. in Pharmacology from the University of Florida in Gainesville, FL. Dr. Standifer was a Post-Doctoral Fellow in the Molecular Pharmacology and Therapeutics Program at Memorial Sloan-Kettering Cancer Center in New York, NY.

John R. Traynor, Ph.D. is the Edward F. Domino Research Professor and Associate Chair for Research in the Pharmacology Department at

the University of Michigan Medical School in Ann Arbor, MI. Dr. Traynor received a Ph.D. in Medicinal Chemistry from the University of Aston in the U.K. Dr. Traynor's post-doctoral research focused on Biochemical Pharmacology at the University of Gottingen in Germany.

David R. Wallace, Ph.D. is a Professor of Pharmacology in the Department of Pharmacology and Physiology, a former Assistant Dean for Research, and Director for Integrative Neuroscience at the Oklahoma State University Center for Health Sciences in Tulsa, OK. Dr. Wallace received a Ph.D. in Pharmaceutical Science from the University of Florida in Gainesville, FL. Dr. Wallace completed Post-Doctoral Fellowships in Pharmacology at the University of Colorado Health Science Center in Denver, CO, and in Pharmacology at the University of Kentucky in Lexington, KY.

Linda Werling, Ph.D. is a Professor of Pharmacology and Physiology, and Professor of Neurological Surgery at the George Washington University School of Medicine and Health Sciences in Washington, DC. Dr. Werling received a Ph.D. in Pharmacology from Duke University in Durham, NC. Dr. Werling was a Post-Doctoral Fellow in the Department of Pharmacology at the Uniformed Services University of the Health Sciences in Bethesda, MD.

SUMMARY OF DISCUSSION

As with the Oklahoma process reviewed in *Glossip*, the State of Ohio employs a three-step lethal injection protocol that begins with a 500 mg injection of midazolam to prevent consciousness and concludes with the administration of a paralytic (that stops respiratory function) and potassium chloride (that stops cardiac function). The Sixth Circuit "agree[d]" that, in the absence of the first drug, the final two steps of the lethal injection protocol "would cause severe pain to a person who is fully conscious." *In re: Ohio Execution Protocol*, No. 17-3076, 2017 WL 2784503, at *2 (6th Cir. June 28, 2017).

At bottom, the parties dispute whether midazolam is an appropriate step-one drug to render the inmate unconscious and incapable of perceiving pain during the lethal-injection process. From a pharmacological perspective, the answer is no.

Amici previously asserted that there is "overwhelming scientific consensus . . . that midazolam is incapable of inducing" the intended "deep, comalike unconsciousness" because of its physical properties and mechanism of action. *Glossip* Amici, 2015 WL 1247193, at *8. As the District Court's findings of fact reflect, the evidence supporting this scientific consensus has grown since *Glossip*. Neither the parties' legal arguments nor dosage can change the material properties of this drug. "An excessive dose of midazolam will not result in unconsciousness." *Id.* From amici's perspective, the Sixth Circuit's decision improperly shuts down the judicial scrutiny that this critical issue deserves.

DISCUSSION

I. Summary of Midazolam Properties from *Glossip* Amici

In *Glossip*, amici identified a number of midazolam's physical properties that categorically distinguish it from barbiturates like thiopental or pentobarbital and render it incapable of producing unconsciousness. These conclusions, and the science supporting them, remain instructive here.

- Midazolam is a fast-acting, short duration benzodiazepine that produces reliable sedative, hypnotic, muscle relaxant, anxiety inhibitory, and anticonvulsant effects. Though it produces sleep and amnesia for short periods, it cannot render a person unconscious or maintain general anesthesia. *Id.* at *10–11 (citations omitted).

- Midazolam's mechanism of action differs from barbiturates and, unlike barbiturates, cannot induce unconsciousness. *Id.* at *11.

- Midazolam, along with GABA[3] ("the key"), the major inhibitory neurotransmitter in the human body, must co-bind with the $GABA_A$ receptor ("the gate") in order "to exert an

[3] For a fuller description of the neurotransmitter γ-aminobutyric acid ("GABA"), how it depresses the central nervous system, and its interaction with benzodiazepines and barbiturates, see *Glossip* Amici, 2015 WL 1247193, at *8–19.

inhibitory effect" on the central nervous system. *Id.* at *13–15 (citations omitted).

- Combining midazolam with GABA and the $GABA_A$ receptor inhibits the central nervous system by increasing the frequency of chloride ion channel opening.

$$[M + G + G_A \rightarrow \text{increase } \textit{frequency} \text{ ion channel opening}]$$

The influx of ions suppresses neuronal firing resulting in "the hallmark sedative and hypnotic effects." *Id.* (citations omitted). In other words, midazolam requires GABA keys to open the ion channel gates temporarily.

- The limited amount of GABA in the body results in a "ceiling effect" on the effectiveness of midazolam. Once the GABA keys run out, midazolam can no longer unlock the $GABA_A$ gates to further increase the chloride ion flow. The effectiveness of benzodiazepines like midazolam plateaus before reaching the level of "general anesthesia." *Glossip* Amici, 2015 WL 1247193, at *19–20 (citations omitted).

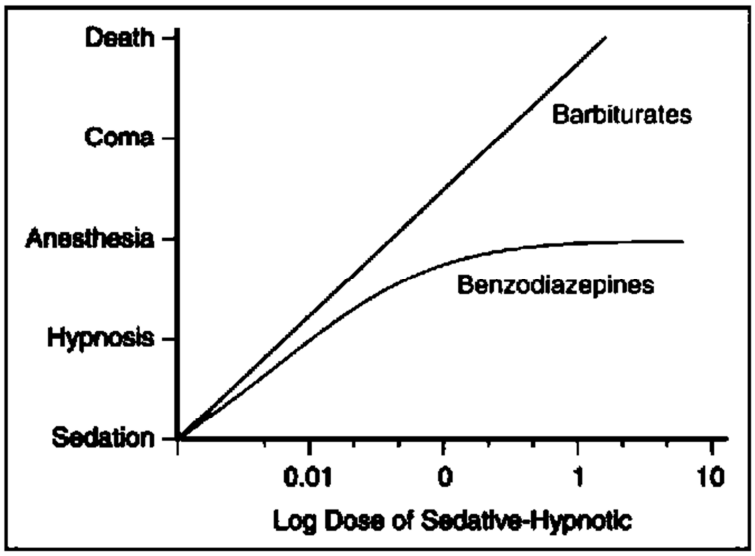
- Barbiturates, by contrast, do not require GABA to inhibit the central nervous system, and do so by affecting the duration of ion channel opening.

$$[B + G_A \rightarrow \text{increase } \textit{duration} \text{ ion channel opening}]$$

Id. at *16–17 (citations omitted). With barbiturates, no GABA key is needed to open the $GABA_A$ gate, and the gate remains open longer.

- Because of their distinct mechanism of action, barbiturates produce steadily more chloride ions such that "increasing doses of barbiturates reliably produce anesthesia, coma, and death." *Id.* at *20 (citations omitted).

Amici again offer this chart to demonstrate the ceiling effect of benzodiazepines, and otherwise adopt the scientific literature cited in their *Glossip* amicus brief.



George M. Brenner & Craig W. Stevens, *Sedative-Hypnotic and Anxiolytic Drugs*, *in Pharmacology* 186, 192 (Fig. 19-3) (4th ed. 2013).

II. The Further Development of these Issues Since *Glossip*

Notwithstanding amici's arguments about midazolam's pharmacological properties, this Court in *Glossip* deferred to the district court's contrary factual conclusion as not clearly erroneous, and on that basis upheld Oklahoma's use of the drug in its lethal injection protocol. 135 S. Ct. at 2739–2740. Yet, the factual issues presented in *Glossip* have continued to mature in the crucible of litigation, with further scientific and experiential evidence bolstering amici's conclusion.

Over the course of a five-day hearing, the District Court heard detailed testimony from plaintiff[4] and defense experts about midazolam's properties. Aided by the adversarial process, the court carefully considered the experts' methods and opinions, as well as their respective critiques of each other's methods. For instance, the court examined:

- Dr. Craig W. Stevens's testimony about the differing mechanisms of action (vis-à-vis GABA) for benzodiazepines like midazolam and barbiturates, and why they are differently classified drugs under the Controlled Substances Act. Pet. App. 87a–90a.

- Dr. Stevens's experiments resulting in his estimate that midazolam reaches its ceiling effect at 228 mg. *Id.* at 90a.

---

[4] Dr. Craig W. Stevens, whose research among others' *amici* rely upon, testified at the hearing on behalf of Plaintiffs.

- Dr. Stevens's opinion, rebutting the defense expert, that the American Society of Anesthesiology differentiates sedation (reduced awareness, response to pain) from general anesthesia (lack of awareness, no response to pain). *Id.* at 114a.

- Dr. Sergio Bergese's opinion that scientific literature "confirm that midazolam cannot induce and maintain a sufficiently deep state of unawareness and being insensate in the presence of painful stimuli." *Id.* at 92a.

- Dr. Stevens's testimony, rebutting the defense expert, explaining that none of the studies cited by the defense show that midazolam produced bispectral index (BIS) brain activity readings in the 40–60 range associated with general anesthesia. *Id.* at 115a–16a; see also *id.* at 93a.

- Dr. Stevens's opinion that Ohio's use of midazolam in its lethal injection protocol made it "highly likely to cause intolerable pain and suffering" from the administration of the second and third drugs; Dr. Bergese's similar opinion that Ohio's use of midazolam "absolutely" posed a substantial risk of experiencing the pain and suffering of execution. *Id.* at 91a, 97a.

These are not idle disagreements with a prior court's conclusions, but the opinions of pharmacological experts supported by reliable

scientific principles. And they explain biological plausibility via physiological mechanism—a key factor in determining the reliability of medical causation opinions under the Bradford Hill factors. See *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193, 1202, 1204 n.7, 1208 (10th Cir. 2002).

The District Court also considered (i) evidence that Florida and Arizona have abandoned using midazolam, and (ii) testimonial accounts of two executions—Ronald Smith (Alabama) and Christopher Brooks (Alabama)—carried out with midazolam since *Glossip*. *Id.* at 83a–84a. Of these, the accounts of the Smith execution relayed that, five minutes after the injection of midazolam, the inmate yanked his arm away from a pinch test, lifted his head, looked around, and moved his arms. *Id.* at 95a–96a. (Smith received a second 500 mg injection of midazolam during his execution.) Dr. Bergese testified that these phenomena reflect a person who is not insensate. *Id.*

From this body of evidence, the District Court concluded that "[p]lainly, midazolam does not have the same pharmacologic effect on persons being executed as the barbiturates thiopental sodium and pentobarbital." Pet. App. 117a. Though the court could not say "precisely why," it still "f[ound] that those administered midazolam (whether in a one injection combination with hydromorphone or in sequence with a paralytic and potassium chloride) take longer to die and exhibit different bodily behaviors in the process. In terms of their respective effects on the human body, deep sedation and general anesthesia are distinct." *Id.*

The District Court's factual findings here echo consensus scientific principles distinguishing between the sedation achieved with a benzodiazepine like midazolam and the deeper level of central nervous system depression required for general anesthesia, and the opportunity for additional fact-finding at a trial would only bolster these conclusions. Judicial fact-finding, like scientific conclusions, ripens from the critical consideration of additional evidence. Cf. *Univ. of Texas v. Camenisch*, 451 U.S. 390, 395 (1981) (explaining that findings of fact made at the preliminary injunction stage "are not binding at trial on the merits" because the "purpose of a preliminary injunction is merely to preserve the relative positions of the parties until a trial on the merits can be held").

In *Glossip*, this Court noted that "challenges to lethal injection protocols test the boundaries of the authority and competency of federal courts," and admonished federal courts not to "embroil [themselves] in ongoing scientific controversies beyond their expertise." 135 S. Ct. at 2740 (quoting *Baze v. Rees*, 553 U.S. 35, 51 (2008)). The District Court here properly acknowledged the pharmacological limits of benzodiazepines. Their physical properties and mechanism of action (including their need for GABA "keys" to be effective) simply do not produce the same sort of prolonged chloride ion release necessary to render someone unconscious as the barbiturates used for general anesthesia.

In sum, midazolam's mechanism of action makes it unsuitable as the first drug in the State of Ohio's three-drug lethal injection protocol because it is incapable of inducing unconsciousness and cannot

prevent the infliction of severe pain. The record of midazolam-protocol executions is profoundly troubling. The petition raises issues of national importance that now, more than ever, deserve this Court's attention and resolution.

CONCLUSION

From a pharmacological perspective, midazolam is not interchangeable with barbiturates like thiopental or pentobarbital. Midazolam is incapable of rendering an inmate unconscious prior to the injection of the second and third drugs in the State of Ohio's lethal injection protocol. Therefore, midazolam is not appropriate for its intended purpose as the first drug in the State of Ohio's three-drug lethal injection protocol.

Respectfully Submitted,

JOHN Q. LEWIS
Counsel of Record
JON W. OEBKER
JENNIFER L. MESKO
CHAD M. EGGSPUEHLER
AMANDA N. JOHNSON
TUCKER ELLIS LLP
950 Main Avenue, Ste. 1100
Cleveland, OH 44113
(216) 592-5000
john.lewis@tuckerellis.com

Counsel for Amici Curiae

July 24, 2017