

No. 17-5198

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IN THE  
**Supreme Court of the United States**

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GARY OTTE, RONALD PHILLIPS,  
AND RAYMOND TIBBETTS,  
*Petitioners,*

v.

RONALD ERDOS, ET AL.,  
*Respondents.*

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

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

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**STATEMENT OF INTEREST  
OF AMICI CURIAE**

Amici curiae, each of whom is listed below, are professors of pharmacology at universities in the United States.<sup>1</sup> 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.<sup>2</sup>

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<sup>1</sup> 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.

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## 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<sup>3</sup> (“the key”), the major inhibitory neurotransmitter in the human body, must co-bind with the GABA<sub>A</sub> receptor (“the gate”) in order “to exert an

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<sup>3</sup> 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<sub>A</sub> 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.

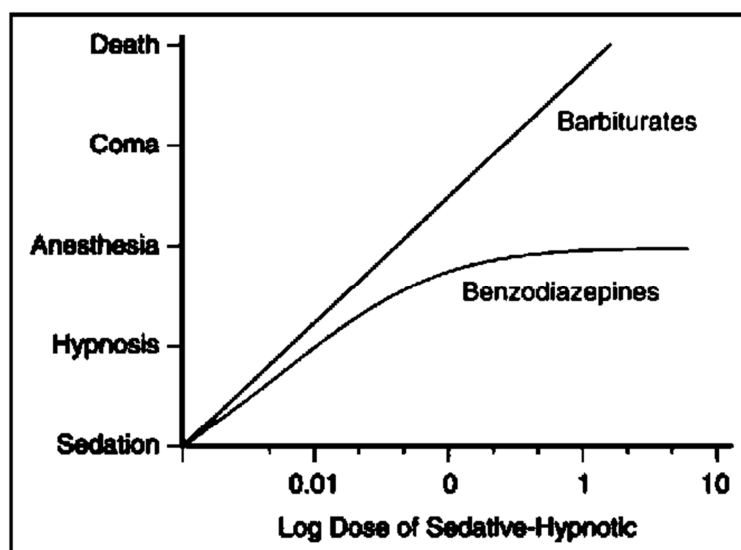
- The limited amount of GABA in the body results in a “ceiling effect” on the effectiveness of midazolam. Once the GABA keys run out, midazolam can no longer unlock the GABA<sub>A</sub> gates to further increase the chloride ion flow. The effectiveness of benzodiazepines like midazolam plateaus before 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<sub>A</sub> 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<sup>4</sup> 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.

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<sup>4</sup> 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,

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