

FILED  
SUPREME COURT  
STATE OF WASHINGTON  
9/13/2021 9:06 AM  
BY ERIN L. LENNON  
CLERK

No. 99956-2

---

**IN THE SUPREME COURT OF THE STATE OF WASHINGTON**

---

CERTIFICATION FROM THE UNITED STATES DISTRICT COURT  
FOR THE WESTERN DISTRICT OF WASHINGTON

IN:

DAVID J. DEARINGER and GANNA P. DEARINGER,  
*Petitioners-Plaintiffs,*

v.

ELI LILLY AND COMPANY,  
*Respondent-Defendant.*

---

**OPENING BRIEF OF PETITIONERS-PLAINTIFFS  
ON CERTIFIED QUESTION**

---

David J. Dearinger, *pro se*  
10218 38th Pl SE  
Lake Stevens, WA 98258-5738  
(425) 220-3690  
daviddearinger@comcast.net

## TABLE OF CONTENTS

	<u>Page</u>
TABLE OF AUTHORITIES .....	ii
I. INTRODUCTION .....	1
II. QUESTION CERTIFIED .....	3
III. STANDARD OF REVIEW .....	4
IV. STATEMENT OF THE CASE .....	5
A. Factual Background .....	6
(1) The Discovery of the Phosphodiesterase-5 Enzyme Inhibitor ....	6
(2) The Marketing of Cialis .....	7
(3) Intracerebral Hemorrhage: the Intentionally Concealed Side-Effect of Cialis .....	11
(4) Plaintiffs' Injury .....	18
V. ARGUMENT .....	19
A. Origin of the Learned Intermediary Doctrine .....	19
(1) Changes to the Doctor-Patient Relationship .....	22
(2) Increase of DTC Advertising .....	24
(3) Cialis is a Recreational Life-Style Drug .....	26
B. Why the Learned Intermediary Doctrine Must Be Re-examined ....	30
(1) The LID Encourages Irresponsible Behavior .....	30
(2) A DTC Exception Would Not Create a Chilling Effect .....	37

C. This Case Demands Authorizing of Punitive Damages .....	38
VI. CONCLUSION .....	39
CERTIFICATE OF COMPLIANCE .....	41
CERTIFICATE OF SERVICE .....	42

## TABLE OF AUTHORITIES

<b>Cases</b>	<b><u>Page</u></b>
<i>Affiliated FM Ins. Co. v. LTK Consulting Servs. Inc.</i> , 556 F.3d 920, 922 (9th Cir. 2009) .....	4
<i>American Geophysical Union v. Texaco Inc.</i> , 802 F. Supp. 1, 27 (S.D.N.Y. 1992) .....	38
<i>Bell Atl. Corp. v. Twombly</i> , 550 U.S. 544, 555-56, 127 S.Ct. 1955, 167 L.Ed.2d 929 (2007) ...	5
<i>Carlsen v. Global Client Solutions, LLC</i> , 171 Wn.2d 486, 493, 256 P.3d 321 (2011) .....	4
<i>Frias v. Asset Foreclosure Servs., Inc.</i> , 181 Wn.2d 412, 420, 334 P.3d 529, 533 (2014) .....	4,5,19
<i>Grimshaw v. Ford Motor Co.</i> 119 Cal. App.3d 757, 174 Cal. Rptr. 348 (1981) .....	28,34
<i>Hruska v. Parke, Davis &amp; Co.</i> , 6 F.2d 536 (8th Cir.1925) .....	20

<i>Larkin v. Pfizer, Inc.</i> , 153 S.W.3d 758, 762 (Ky.2004) .....	20
<i>Marcus v. Specific Pharms.</i> , 191 Misc. 285, 77 N.Y.S.2d 508 (N.Y.Sup.Ct.1948) .....	20
<i>Odgers v. Ortho Pharm. Corp.</i> , 609 F.Supp. 867, 873 n. 12 (E.D.Mich.1985) .....	20
<i>Perez v. Wyeth Lab. Inc.</i> , 161 N.J. 1, 24, 734 A.2d 1245, 1255 (1999) .....	23,24,29
<i>State ex rel. Johnson &amp; Johnson v. Karl</i> , 220 W.Va. 463, 647 S.E.2d 899, 910 (2007) .....	23,24,25
<i>Stafford v. Wallace</i> , 258 U.S. 495, 516, 42 S.Ct. 397, 66 L.Ed. 735 (1922) .....	30
<i>Sterling Drug, Inc. v. Cornish</i> , 370 F.2d 82, 85 (8th Cir.1966) .....	19
<i>Swift &amp; Co. v. United States</i> , 196 U.S. 375, 399, 25 S.Ct. 276, 49 L.Ed. 518 (1905) .....	30
<i>Terhune v. A.H.Robins Co.</i> , 90 Wn.2d 9, 577 P.2d 925 (1978) .....	4,17,28

## **Statutes**

21 U.S.C. ch. 9 § 301 <i>et seq.</i> (1938) .....	25
21 U.S.C. §301 (1997) .....	25
28 U.S.C. § 1332(a)(1) .....	5
RCW 2.60.020 .....	2

RCW 7.72 <i>et. seq</i> .....	5
-------------------------------	---

## **Rules and Regulations**

Fed.R.Civ.P. 12(b)(6) .....	5,19
RAP 10.4(e) .....	2

## **Other Authorities**

<i>Allen, Medicine Goes Madison Avenue: An Evaluation of the Effect of Direct-to-Consumer Pharmaceutical Advertising on the Learned Intermediary Doctrine</i> , (1997), 20 Campbell L. Rev. 113 .....	37
<i>Angell, Relationships with the Drug Industry: Keep at Arm's Length</i> , 2009, 338 Brit. Med. J. b222 (2009) .....	36
Eli Lilly and Company, Annual Reports <a href="https://investor.lilly.com/financial-information/annual-reports">https://investor.lilly.com/financial-information/annual-reports</a>	8,9,33,35
Food and Drug Administration (FDA) website <a href="https://www.fda.gov/drugs/prescription-drug-advertising/background-drug-advertising">https://www.fda.gov/drugs/prescription-drug-advertising/background-drug-advertising</a> .....	21
<i>Feidman, Impotence and its medical and psychosocial correlates: Massachusetts results of the male aging study</i> , 1994, Journal of Urology, 151, 54-61 .....	7
Goldacre, <i>Bad Pharma</i> , 2013, Fourth Estate, London .....	1
<i>Goldstein, Burnett, Rosen; The Serendipitous Story of Sildenafil: An Unexpected Oral Therapy for Erectile Dysfunction</i> , Sexual Medicine Reviews. 2019, 7 (1): 115–128 .....	6

Government Accounting Office (GAO)- 07-54 Prescription Drugs: Improvements Needed in FDA'S Oversight of Direct-To-Consumer Advertising 5, 12 (Nov. 2006) ...	34
Kirsch, Donald R., <i>How to Discover a New Drug (And Why It's So Difficult)</i> , Salon.com, October 13, 2018 .....	2
Moore & Newton, <i>Prescription Drug Advertising on the Internet: A Proposal for Regulation</i> , 2 W. Va. J.L. & Tech. 1.1, ¶ 3 (Feb. 14, 1998) .....	24
National Center for Biotechnology Information Website <a href="https://www.ncbi.nlm.nih.gov">https://www.ncbi.nlm.nih.gov</a> .....	39
Palumbo & Mullins, <i>The Development of Direct-to-Consumer Prescription Drug Advertising Regulation</i> , 57 Food & Drug L.J. at 423 .....	25
Restatement (Second) of Torts § 402A cmt. k (Am. Law Inst. 1965) .....	27,28,30
Rosok, <i>Direct-to- Consumer Advertising of Prescription Drugs: After a Decade of Speculation, Courts Consider Another Exception to the Learned Intermediary Rule</i> , (2000), 24 Seattle U. L. Rev. 629 .....	37
Schwartz, <i>Consumer-Directed Prescription Drug Advertising and the Learned Intermediary Rule</i> , 40 Food Drug Cosm. L.J. 135, 136 (1985) .....	19
Stolberg, <i>Faulty Warning Labels Add to Risk in Prescription Drugs</i> , N.Y. Times, June 4, 1999, at A27 .....	22
Taylor, The Pharmaceutical Industry and the Future of Drug Development, <i>Pharmaceuticals in the Environment</i> , 2015, 1-33 .....	1

Trivedi, J.K., <i>Contemporary Issues in Management of Impotence</i> , 1998, Indian J. Psychiat, 40 (3), 199-200 .....	8
Wentzell, Labuski, <i>Role of Medical Anthropology in Understanding Cultural Differences in Sexuality</i> , 2020, Cham: Springer International Publishing, 23-35 .....	26

## Appendix

- Monastero, Pipia, Camarda; *Intracerebral Haemorrhage Associated With Sildenafil Citrate*, J Neurol, 2001, 248:141-142 ..... APPENDIX 1,2
- Steeves, Jones, Ecker; *Coital Hemorrhage of an Arteriovenous Malformation after Premedication with Tadalafil (Cialis)*, J Stroke and Cerebrov Diseas, 2005, 14:4, 179-181 ..... APPENDIX 3,4,5
- Hellstrom; *Visual Field Defect and Intracerebral Hemorrhage Associated With Use of Vardenafil (Levitra)*, 2006, Neurology, 66:293 ,,,,,,, ,,, ,,, APPENDIX 6,7,8
- Alpsan, Bebek, Ciftci; *Intracerebral hemorrhage Associated With Sildenafil Use: A Case Report*, 2008, J Neurol, 255:932–933 ..... APPENDIX 9,10
- Gazzeri, Neroni, Galarza, Esposito; *Intracerebral Hemorrhage Associated with Use of Tadalafil (Cialis)*, Neurology 2008;70:1289-1290 ... APPENDIX 11,12,13
- Byoun, Lee, Yi; *Subarachnoid Hemorrhage and Intracerebral Hematoma due to Sildenafil Ingestion in a Young Adult*, Jour. of Korean Neuro. Soc. 2010; 47:210-212 ..... APPENDIX 14,15,16
- Sheikh-Taha, Alaywa; *Subarachnoid hemorrhage associated with tadalafil*, Am J Health-Syst Pharm, 2011, 68:1195-1195 ..... APPENDIX 17,18
- Antar, Koksal Sutpideler, Baran, *Subarachnoid and Intracerebral Hemorrhage After Alcohol Ingestion and Illicit Use of Sildenafil*, Turk Neurosurg, 2015, 25:3, 485-487 ..... APPENDIX 19,20,21

Adiga, Edriss, and Nugent; *Intracranial Aneurysm and Sildenafil*, Proc (Bayl Univ Med Cent) 2016; 29(2):178–180 ..... APPENDIX 22,23,24

Nakamura, Watanabe, Harada; *Acute Intracranial and Spinal Subdural Hematoma Associated with Vardenafil*, J Stroke and Cerebrov Diseas, 2018, 27:9, 201-202 ..... APPENDIX 25-26

Lucchese, Dhaliwal, Kaur, Qi; *A Case of Recurrent Lobar Intracerebral Hemorrhage in the Setting of Phosphodiesterase-5 Inhibitor Use*, Missouri Medicine, 2019 116:5 ..... APPENDIX 27,28,29,30



## I. INTRODUCTION

The pharmaceutical industry is unlike any other commercial enterprise. It is replete with contradictions; for example, while the pharmaceutical industry has prolonged life and alleviated suffering for more than a century, it is identified in opinion surveys as one of the least trusted entities, right alongside nuclear power plants.<sup>1/</sup> And while the pharmaceutical industry is one of the riskiest business enterprises in which to invest, the general public views “Big Pharma”<sup>2/</sup> as excessively profitable.<sup>3/</sup> No other industry in the world demands more financial risk than the pharmaceutical industry. Every new drug discovery requires, on average, a financial investment of about \$1.5 billion and it takes about 14 years before any new drug, assuming a new drug is actually developed, can be approved for

---

<sup>1/</sup> See Taylor, “The Pharmaceutical Industry and the Future of Drug

<sup>2/</sup> “Big Pharma” was coined as a pejorative term to describe the large drug manufacturers of the pharmaceutical industry sector. See Goldacre, *Bad Pharma*, 2013, Fourth Estate, London.

<sup>3/</sup> Taylor, *supra*.

marketing.<sup>4/</sup> One can certainly appreciate the obstacles confronting the highly speculative pursuit of new drug therapies.

The Petitioners-Plaintiffs (hereinafter “Plaintiffs” or “the Dearingers,” *see RAP 10.4(e)*<sup>5/</sup>) are not unmindful of the challenges facing the Respondent-Defendant (hereinafter “Defendant” or “Eli Lilly & Co.”), indeed the entire pharmaceutical industry, in responding to the perpetual demand for better medicines. Nevertheless, as with any business concern operating in the United States, it must operate ethically and responsibly; Defendant clearly has not done so, as this case will show.

Plaintiffs herein will demonstrate for the Court that Defendant had foreknowledge that its product has a dangerous

---

<sup>4/</sup> Kirsch, Donald R., *How to Discover a New Drug (And Why It's So Difficult)*, Salon.com, October 13, 2018.

<https://www.salon.com/2018/10/13/how-to-discover-a-new-drug-and-why-its-so-difficult/> (last visited August 18, 2021).

<sup>5/</sup> RAP 10.4(e) provides in pertinent part: “. . . It promotes clarity to use the designations used in the lower court, [or] the actual names of the parties . . .”

side-effect but chose to conceal that foreknowledge from, not only the public at large, but from the prescribing physicians as well; Defendant did so because it knew that its tortuous conduct would be sheltered from any legal consequences by the learned intermediary doctrine (hereinafter “LID”).<sup>6/</sup> Defendant has abused the special status bestowed upon it by the courts of this nation with the advent of the LID.

Perhaps many of the criticisms directed toward the pharmaceutical industry are warranted. Cases such as this should merit an exception to the LID.

## **II. QUESTION CERTIFIED TO THE SUPREME COURT**

To assist in determining whether the Defendant is entitled, under Washington law, to application of the LID as a defense, United States District Judge John C. Coughenour has

---

<sup>6/</sup> In this brief the terms LID and LIR (learned intermediary rule) are used interchangeably.

certified, pursuant to RCW 2.60.020 (1965), the following question to the Supreme Court of the State of Washington:

Is a manufacturer, that promotes a prescription drug through “direct-to-consumer” marketing, still exempt from warning the consumer of that drug’s dangerous side effects under the “Learned Intermediary Doctrine” adopted by the State of Washington in *Terhune v. A.H. Robins Co.*, 577 P.2d 925 (Wash. 1978)?<sup>7/</sup>

Eli Lilly and Company has invoked the LID as a defense to shield itself for its refusal to warn consumers and physicians about the dangerous side effects of its product Cialis.

### **III. STANDARD OF REVIEW**

This Court reviews certified questions of law *de novo*.

*Frias v. Asset Foreclosure Servs., Inc.*, 181 Wn.2d 412, 420, 334 P.3d 529, 533 (2014), citing *Carlsen v. Global Client*

---

<sup>7/</sup> Judge Coughenour added the following: “The Court does not intend Plaintiffs’ framing of the question to restrict the Washington Supreme Court’s consideration of any other issues that it determines are relevant. Moreover, the Washington Supreme Court may, in its discretion, reformulate the question in whatever manner it finds most appropriate. See *Affiliated FM Ins. Co. v. LTK Consulting Servs. Inc.*, 556 F.3d 920, 922 (9th Cir. 2009).” Order of July 6, 2021 (Dkt. No. 28).

*Solutions, LLC*, 171 Wn.2d 486, 493, 256 P.3d 321 (2011).

The Court considers the questions presented “in light of the record certified by the federal court.” *Id.* Because the federal court has certified the question here in connection with a motion for dismissal for failure to state a claim on which relief may be granted pursuant to Fed.R.Civ.P. 12(b)(6), all facts alleged in the complaint must be accepted as true. *Frias, supra*, citing *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 555-56, 127 S.Ct. 1955, 167 L.Ed.2d 929 (2007).

#### **IV. STATEMENT OF THE CASE**

This case comes before the Court on a certified question from the United States District Court for the Western District of Washington. The underlying civil action was initiated by Plaintiffs <sup>8/</sup> under that court’s diversity jurisdiction, 28 U.S.C. § 1332(a)(1) (Defendant is an Indiana Corporation), and under Washington’s Products Liability Act, RCW 7.72 *et seq.*

---

<sup>8/</sup> *Dearinger v. Eli Lilly & Co.*, No. C21-00060-JCC (W.D.Wash. 2021).

(hereinafter “WPLA”). Mr. Dearinger was injured by a prescription drug manufactured and marketed by the Defendant.

## A. Factual Background

### **(1) Discovery of the Phosphodiesterase-5 Enzyme Inhibitor**

The first phosphodiesterase-5 enzyme inhibitor (hereinafter “PDE<sub>5</sub> inhibitor”) was discovered quite by accident in 1989 by the Pfizer Corporation <sup>9/</sup> while seeking a drug therapy to treat angina pectoris. <sup>10/</sup> While the PDE<sub>5</sub> inhibitor Pfizer tested failed as an effective treatment for angina pectoris, “a very observant nurse” discovered that some of the male subjects were embarrassed by an unexpected benefit <sup>11/</sup> of the PDE<sub>5</sub> inhibitor being tested. <sup>12/</sup>

---

<sup>9/</sup> The Pfizer Corporation is not involved with this litigation.

<sup>10/</sup> Goldstein, Burnett, Rosen; *The Serendipitous Story of Sildenafil: An Unexpected Oral Therapy for Erectile Dysfunction*, 2019, Sexual Medicine Reviews. 7 (1): 115–128.

<sup>11/</sup> Inasmuch that maintaining decorum is essential to the orderly administration of justice, Plaintiffs will endeavor to respect the dignity of this honorable Court and refrain from stating the obvious.

The PDE<sub>5</sub> inhibitor was patented by Pfizer under the generic name Sildenafil in 1996 and was approved by the Food and Drug Administration (hereinafter “FDA”) for sale to the public as a treatment for erectile dysfunction (hereinafter “ED”) on March 27, 1998 under the registered trademark Viagra®.

## **(2) The Marketing of Cialis**

Defendant patented its own version of the PDE<sub>5</sub> inhibitor called Tadalafil, which was approved by the FDA on November 21, 2003 (Drug Application #021368) for manufacture and sale under the registered trademark Cialis®<sup>13/</sup> (the prescription drug at issue in this case) also for the treatment of ED.<sup>14/</sup>

---

<sup>12/</sup> Goldstein, *supra*.

<sup>13/</sup> The most notable distinction between Viagra and Cialis is the duration of the therapeutic effectiveness, which is 36 hours for Cialis and only 5 hours for Viagra.

<sup>14/</sup> The FDA later approved Cialis® for the treatments of pulmonary arterial hypertension (PAH) on May 22, 2009 and benign prostatic hyperplasia (BPH) on October 6, 2011.

Based upon the available cultural research, Defendant knew that the PDE<sub>5</sub> inhibitor could possibly become the most sought-after life-style drug ever discovered,<sup>15/</sup> and in view of the inordinately high importance our generation places upon connubial relations,<sup>16/</sup> Defendant wasted no time in announcing to its shareholders that it was beginning an aggressive new “direct-to-consumer” (hereinafter “DTC”) advertising campaign, independent of prescribing physicians.

In answering the question:

How can [Eli] Lilly [and Co.] do justice to so many new products all at once? And, with so many launches, can you afford to grow earnings in 2004?

Defendant answered thus:

---

<sup>15/</sup> A 1994 study estimated that 10-20 million people in America suffer from impotence. Feidman, HA, Goldstein, I. & Hatzfchrfstou, D.G., *Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study*, 1994, Journal of Urology, 151, 54-61.

<sup>16/</sup> “Sex is a man's second strongest instinct, after that of survival. This means that if a man's life is not immediately imperiled, the next thing he will automatically think of is sex. This is a fundamental reality of life and explains why sexual impotence or erectile dysfunction is associated with so much of distress, guilt, shame and embarrassment.” Trivedi, J.K., *Contemporary Issues in Management of Impotence*, 1998, Indian J. Psychiatr, 40 (3), 199-200,

This year, we are investing aggressively to market Cialis in the U.S. and will have additional new expenditures when we launch Cymbalta and duloxetine SUI, but, for the most part, the infrastructure investments needed to support these launches are already in our base.

*Eli Lilly and Company 2003 Annual Report*, at page 4. <sup>17/</sup>

Cialis was launched in 2003 in several markets outside the U.S. by Lilly and ICOS. Cialis was launched in the U.S. in early December 2003. Cialis had total sales of \$203.3 million in 2003. Of this total, \$73.5 million represent sales in our exclusive territories and are reported in our net sales. The remaining Cialis sales relate to the joint-venture territories of Lilly ICOS LLC (North America and Europe) and are reported in the Lilly ICOS joint-venture income statement along with related expenses. We report our 50 percent share of the operating results of the joint venture in our net other income. In early 2004, Lilly ICOS began a *direct-to-consumer* advertising campaign in the U.S. We will continue to increase our *direct-to-consumer* advertising activities in print and on television.

*Id.* at page 11 (emphasis added).

Soon afterward the nation's airwaves were inundated with news of Defendant's "Fountain of Youth." <sup>18/</sup> Thirty

---

<sup>17/</sup> <https://investor.lilly.com/financial-information/annual-reports> (last visited August 6, 2021).

second television commercials began appearing in prime-time with bikini clad young women <sup>19/</sup> reminding men of how good life used to be. The commercials would contain a one-sentence warning about priapism (which most men would consider an inducement rather than a warning) but not a single word about the dangerous side-effect of intracerebral hemorrhage (hereinafter “ICH”).

//

//

//

---

<sup>18/</sup> The “Fountain of Youth” is the mythical wellspring first mentioned by the ancient Greek writer/historian Herodotus in about 430 B.C. Bathing in, or swallowing, its waters would cease, even reverse, aging. Its legend endured onto 1513 A.D. and the Spanish conquistador Ponce de León, whose voyage to discover the epic fountain in Florida was referenced in Nathaniel Hawthorne’s 1837 short story collection *Twice-Told Tales*: “Dr. Heidegger’s Experiment.” The Fountain has become a metaphor for humankind’s incessant desire to regain the lost springtime of life and represents what everyone desires: hope for a longer and better life. The legend of such a fountain yet lives on into the twenty-first century, kept alive by direct-to-consumer marketing of recreational pharmaceuticals like PDE<sub>5</sub>.

<sup>19/</sup> Every Madison Avenue ad executive knows that sex sells, especially where the product being sold is sex *itself*. Those sexy ads are not designed to appeal to a potential customer’s intellect, but rather to his (the target audience is men) baser instincts.

### **(3) Intracerebral Hemorrhage: the Intentionally Concealed Side Effect of Cialis**

Reports began to surface from all over the world that the PDE<sub>5</sub> inhibitor is not nearly as safe as the pharmaceutical industry has portrayed in its DTC advertising; case studies reveal that PDE<sub>5</sub> inhibitors cause ICH.

In as early as 2001 a letter was published in the Journal of Neurology by four Italian neurologists documenting a 67 year-old dentist who suffered an ICH after ingesting a 25 mg Viagra® tablet. Monastero, Pipia, Camarda; *Intracerebral Haemorrhage Associated With Sildenafil Citrate*, J Neurol, 2001, 248:141-142. (Attached hereto as Appendix 1-2). <sup>20/</sup>

---

<sup>20/</sup> Plaintiffs acknowledge the hard work done by employees of the Washington State Library System, particularly reference librarians Kelsey Smith (Washington State Library, Olympia, Washington) and Mary Whisner (Gallagher Law Library, University of Washington School of Law, Seattle, Washington), who provided copies of the journal articles reproduced in the Appendix section of this brief. The 11 studies appearing in the Appendix are not exhaustive. There are several more studies available that document the risk for intracranial hemorrhage when ingesting PDE<sub>5</sub> inhibitors, some cited in the bibliography section of each of these studies. Plaintiffs hope the 11 examples provided in the Appendix will suffice to advise the Court of the abundance of evidence available to alert the Defendant as early as 2001, that ICH is a serious risk

In 2005 researchers from the Neurology and Neurosurgery Departments of the Mayo Clinic in Rochester, Minnesota reported that a 59 year-old man suffered an ICH after taking a 10 mg Cialis® tablet. Steeves, Jones, Ecker; *Coital Hemorrhage of an Arteriovenous Malformation after Premedication with Tadalafil (Cialis)*, J Stroke and Cerebrov Diseas, 2005, 14:4, 179-181. (Appendix 3-5).

In 2006 a response to the article: McGee HT, Egan RA, Clark WM. *Visual field defect and intracerebral hemorrhage associated with use of vardenafil (Levitra)*. Neurology 2005; 64:1095–1096, a Dr. Hellstrom took issue with the causality of the subject's ICH:

The issue of causality and association of vardenafil with ICH may be difficult to ascertain in this patient in the McGee article because of the following confounders: although rare, ICH has been reported for all 3 PDE-5 inhibitors; the specific doses and duration of therapy with the previously used PDE -5 inhibitor (sildenafil) were not given; although no history of drug use was mentioned, a toxicology screen was not conducted;

---

when ingesting PDE<sub>5</sub> inhibitors that should have been included in the Defendant's DTC advertisements and warning literature.

and a multiplicity of risk factors are involved in the etiology of ICH3.

To that statement the authors responded:

We appreciate Dr. Hellstrom's response to our article and agree with all of his points. When assessing whether or not a side effect is related to a medication, timing of onset of symptoms in relation to ingestion of drug is important in addition to whether symptoms recur when the patient takes the drug again. Today, serious side effects of medications are difficult to prove since patients are reluctant to rechallenge themselves with a drug they believe was implicated in causing their symptoms. Therefore, we are left with the timing of onset of symptoms to ingestion.

Although we, the authors, are at a loss to hypothesize a mechanism of causation of ICH in our patient, our intention was to alert the medical community to this possible association through publication.

Hellstrom; *Visual Field Defect and Intracerebral Hemorrhage Associated With Use of Vardenafil (Levitra)*, 2006, Neurology, 66:293. (Appendix 6-8).

In 2008 another letter was published in the Journal of Neurology, this time by six Turkish Neuroscientists that were members of the Istanbul University Medical Faculty

documenting a 62 year-old right-handed man that was admitted to their hospital after he suffered left-side paralysis from an ICH about an hour after ingesting 50 mg of Viagra. Alpsan, Bebek, Ciftci; *Intracerebral hemorrhage Associated With Sildenafil Use: A Case Report*, 2008, J Neurol, 255:932–933. (Appendix 9-10).

Also in 2008 four Italian Neurologists of the Department of Neurosurgery at the San Giovanni Addolorata Hospital in Rome, Italy documented, in the journal Neurology, a 70 year-old man that suffered an ICH one hour after ingesting two 20 mg (40 mg total) Cialis® tablets. Gazzeri, Neroni, Galarza, Esposito; *Intracerebral Hemorrhage Associated with Use of Tadalafil (Cialis)*, Neurology 2008;70:1289-1290. (Appendix 11-13).

In 2010 three Korean neurosurgeons at the Hanyang University Medical Center published in the Journal of the Korean Neurosurgical Society a case involving a 33 year-old man who “had been healthy and free of any significant medical

history” who suffered an ICH an half-hour after ingesting a 50 mg Viagra tablet. Byoun, Lee, Yi; *Subarachnoid Hemorrhage and Intracerebral Hematoma due to Sildenafil Ingestion in a Young Adult*, Jour. of Korean Neuro. Soc. 2010; 47:210-212. (Appendix 14-16).

In 2011 a cardiologist and a pharmacologist from the Lebanese American University in Byblos, Lebanon reported in the American Journal of Health-System Pharmacy a case involving a 45 year-old “previously healthy man” who suffered a subarachnoid hemorrhage a few hours after taking one 20 mg Cialis® tablet. Sheikh-Taha, Alaywa; *Subarachnoid hemorrhage associated with tadalafil*, Am J Health-Syst Pharm, 2011, 68:1195-1195. (Appendix 17-18).

In 2015 four Turkish neuroscientists from the Istanbul Research and Education Hospital reported in the Journal of Turkish Neurosurgery a case of a 42 year-old man that died after he suffered both a subarachnoid and a cerebral hemorrhage after ingesting alcohol and a 50 mg Viagra® tablet

and then had sexual intercourse. Antar, Koksal Sutpideler, Baran, *Subarachnoid and Intracerebral Hemorrhage After Alcohol Ingestion and Illicit Use of Sildenafil*, Turk Neurosurg, 2015, 25:3, 485-487. (Appendix 19-21).

In 2016 three neurologists from the Texas Tech University Health Science Center in Lubbock, Texas reported in the Journal of the Baylor University Medical Center that a 42 year-old diabetic man with hypertension suffered a rupture of a saccular intracranial aneurysm, which led to a subarachnoid hemorrhage, after ingesting 100 mg of Viagra®. Adiga, Edriss, and Nugent; *Intracranial Aneurysm and Sildenafil*, Proc (Baylor Univ Med Cent) 2016; 29(2):178–180. (Appendix 22-24).

In 2018 six Japanese neurologists from the Department of Neurology at the Sendai Medical Center in Sendai, Japan report that “[a] 28-year-old man with no medical history” suffered an intracranial and spinal subdural hematoma after ingesting 10 mg of vardenafil, (a PDE<sub>5</sub> inhibitor manufactured by Bayer Pharmaceuticals, *et al* under the names Levitra®,

Staxyn®), and Vivanza®). Nakamura, Watanabe, Harada; *Acute Intracranial and Spinal Subdural Hematoma Associated with Vardenafil*, J Stroke and Cerebrov Diseas, 2018, 27:9, 201-202. (Appendix 25-26).

In 2019 three neurology professors of the Columbia School of Medicine at the University of Missouri in Columbia, Missouri, and one professor from the Government Medical College in Patiala, India reported to the Journal of the Missouri State Medical Association the case of “a 69 year-old white male who experienced two episodes of intracranial lobar hemorrhage temporarily associated with PDE-5 use.” Lucchese, Dhaliwal, Kaur, Qi; *A Case of Recurrent Lobar Intracerebral Hemorrhage in the Setting of Phosphodiesterase-5 Inhibitor Use*, Missouri Medicine, 2019 116:5. (Appendix 27-30). Near the end of this published study is a paragraph that explains Plaintiffs’ case in a nutshell:

This case bolsters existing evidence that PDE-5 inhibitors as a class should be viewed with caution. As of publication, FDA warns against possible

cardiovascular adverse reactions, hearing loss, hypotension, and priapism, *however does not warn that ICH may be [sic] possible side effect.*

*Id.* (emphasis added)(Appendix 30).

To summarize: Defendant knew as early as the year 2001, two years before the FDA approved Cialis, that ingestion of PDE<sub>5</sub> inhibitors could result in ICH.

#### **(4) Plaintiffs' Injury**

Because Defendant refused to warn the public (or even warn prescribing physicians) that Cialis can cause an ICH, Mr. Dearinger unknowingly ingested Cialis and two hours later suffered an ICH which left him hemiplegic with left side paralysis; Mr. Dearinger has lost the use of his left arm and leg.

Plaintiffs filed a civil complaint against Eli Lilly & Co. alleging negligent design, negligent failure to warn, breach of warranty, and a common law claim for Mrs. Dearinger's loss of consortium. Eli Lilly & Co. countered with a motion to

dismiss, pursuant to Fed.R.Civ.P. 12(b)(6),<sup>21/</sup> citing the LID as its defense.

## V. ARGUMENT

### A. Origin of the Learned Intermediary Doctrine

The LID finds its origin in the common law. Fifty-five (55) years ago the LID was born to a panel of the Eighth Circuit in the case of *Sterling Drug, Inc. v. Cornish*, 370 F.2d 82, 85 (8th Cir.1966)<sup>22/</sup> (“the purchaser's doctor is a *learned intermediary* between the purchaser and the manufacturer”)

---

<sup>21/</sup> Insofar as the certified question here is in connection with a motion for dismissal for failure to state a claim on which relief may be granted pursuant to Fed.R.Civ.P. 12(b)(6), all facts alleged in the complaint must be accepted as true. *Frias v. Asset Foreclosure Servs., Inc.*, *supra*.

<sup>22/</sup> The 1966 Eighth Circuit panel was comprised of Circuit Judge Charles Joseph Vogel, born in 1898, Circuit Judge Pat Mehaffy, born in 1904, and District Judge Edward Joseph McManus of the Northern District of Iowa sitting by designation, born in 1920. All three judges lived during a time when the decision to take a prescription drug was “exclusively a matter for medical judgment.” Schwartz, *Consumer-Directed Prescription Drug Advertising and the Learned Intermediary Rule*, 40 Food Drug Cosm. L.J. 135, 136 (1985).

(emphasis added)), <sup>23/</sup> during a time when mass media was in its infancy; televisions were in fewer homes and the television commercial was a relatively new concept. <sup>24/</sup> Advertising of prescription drugs on television was inconceivable 1966. In those days drug companies marketed their prescription drugs only to licensed physicians because only licensed physicians were aware of the existence of most prescriptions medications, thus advertising dollars were focused on the audience that made

---

<sup>23/</sup> The Eighth Circuit flirted with the idea of exempting drug manufacturers from strict liability as early as 1925, yet found the defendant drug company in that case nevertheless liable in *Hruska v. Parke, Davis & Co.*, 6 F.2d 536 (8th Cir.1925). But the first actual case in the nation where a drug manufacturer was found to have fulfilled its duty to warn by warning only the physician was in 1948 with *Marcus v. Specific Pharms.*, 191 Misc. 285, 77 N.Y.S.2d 508 (N.Y.Sup.Ct.1948), as noted by *Odgers v. Ortho Pharm. Corp.*, 609 F.Supp. 867, 873 n. 12 (E.D.Mich.1985) and *Larkin v. Pfizer, Inc.*, 153 S.W.3d 758, 762 (Ky.2004).

<sup>24/</sup> The Federal Communications Commission (FCC) adopted Rules and Standards for commercial broadcast television effective as of July 1, 1941 which permitted the world's first "television commercial" that was aired on the same day. A ten second spot was purchased for \$9 by the Bulova Watch Company and played in the New York City market immediately before a baseball game between the Brooklyn Dodgers and the Phillies on the WNBC Network (owned by RCA) at 2:29 p.m. On that simplistic first TV *commercial* an audio message "America runs on Bulova time" was heard with a video of a still image of a clock face reading "8:00" with the inscription "Bulova Watch Time" superimposed over a still image of the continental United States.

the ultimate decision to prescribe <sup>25/</sup> a medication; the licensed physicians.

Everything changed twenty years later when Big Pharma learned that profits could increase through DTC advertising which, in essence, bypasses the prescribing physician by diverting their advertising dollars away from the family doctor and targeting the patient directly:

Direct-to-consumer (DTC) advertising is a relatively new area of prescription drug promotion. No federal law has ever banned DTC advertising. Until the mid-1980s, drug companies gave information about prescription drugs only to doctors and pharmacists. When these professionals thought it appropriate, they gave that information to their patients. However, during the 1980s, some drug companies started to give the general public more direct access to this information through DTC ads.

Food and Drug Administration (FDA) website. <sup>26/</sup>

---

<sup>25/</sup> The category of drugs requiring a “prescription” from a licensed physician was established under the Federal Food, Drug, and Cosmetic Act of 1938 with the creation of the Food and Drug Administration (FDA) to regulate prescription drugs. 21 U.S.C. ch. 9 § 301 *et seq.* (1938).

<sup>26/</sup> <https://www.fda.gov/drugs/prescription-drug-advertising/background-drug-advertising>, (last visited September 9, 2021).

Prescription drugs have entered a new era making the LID obsolete. While the LID may have been valid at one time, it is no longer because drug companies now utilize DTC advertising where their drugs are now being advertised in 30 second television commercials directed straight to the patient, and thereby bypassing prescribing physicians.

### **(1) Changes To The Doctor-Patient Relationship**

As Defendant is undoubtedly aware, Health Management Organizations (HMOs) and managed care have greatly reduced the amount of time the family physician spends with each patient.

[B]ecause managed care has reduced the time allotted per patient, physicians have considerably less time to inform patients of the risks and benefits of a drug. Stolberg, *Faulty Warning Labels Add to Risk in Prescription Drugs*, N.Y. Times, June 4, 1999, at A27. "In a 1997 survey of 1,000 patients, the F.D.A. found that only one-third had received information from their doctors about the dangerous side effects of drugs they were taking." *Ibid.*

*Perez v. Wyeth Lab. Inc.*, 161 N.J. 1, 24, 734 A.2d 1245, 1255 (1999).

When the Supreme Court of New Jersey accepted the DTC advertising exception to the LID, it listed four premises upon which the LID was based:

- (1) reluctance to undermine the doctor patient-relationship;
- (2) absence in the era of "doctor knows best" of need for the patient's informed consent;
- (3) inability of drug manufacturer to communicate with patients; and
- (4) complexity of the subject; are all (with the possible exception of the last) absent in the direct-to-consumer advertising of prescription drugs.

*Perez, supra.* In summary, the reasons why courts have adopted the LID in the first place have all but disappeared with the advent of DTC advertising. "Consumer-directed advertising of pharmaceuticals thus belies each of the premises on which the learned intermediary doctrine rests." *State ex rel. Johnson & Johnson v. Karl*, 220 W.Va. 463, 647 S.E.2d 899, 910 (2007).

//

//

## **(2) Increase of DTC Advertising**

In following the reasoning of New Jersey in *Perez v. Wyeth Lab. Inc., supra*, the Supreme Court of West Virginia rejected the LID *outright* in *State ex rel. Johnson & Johnson v. Karl, supra*. The West Virginia Supreme Court noted the unmistakable spike in advertising dollars spent by drug manufacturers when the FDA offered them guidance on how to market directly to consumers:

In 1997, the FDA issued draft guidelines intended to supplement the regulations regarding broadcast advertisements. These guidelines led to a rapid proliferation of a newer, more informative broadcast advertisement, allowing the manufacturers to include both the product name and indication. The guidelines recommended that drug manufacturers provide a means for consumers to obtain more information (e.g. an Internet Web page address).

Moore & Newton, *Prescription Drug Advertising on the Internet: A Proposal for Regulation*, 2 W. Va. J.L. & Tech. 1.1, ¶ 3 (Feb. 14, 1998) (emphasis added) (footnote omitted), quoted

*in State ex rel. Johnson & Johnson v. Karl, supra*, 647 S.E.2d at 908.

The massive increase in direct-to-consumer advertising in recent years is striking. One commentator has provided the following table tracking spending on direct-to-consumer, or DTC, spending from the year 1989 to the year 2001:

Year DTC Spending

1989	\$ 12 million
1990	\$ 48 million
1991	\$ 56 million
1992	\$156 million
1993	\$166 million
1994	\$242 million
1995	\$313 million
1996	\$595 million
1997	\$844 million
1998	\$1.17 billion
1999	\$1.58 billion
2000	\$2.24 billion
2001	\$2.38 billion

Palumbo & Mullins, The Development of Direct-to-Consumer Prescription Drug Advertising Regulation, 57 Food & Drug L.J. at 423 (footnotes omitted).

*State ex rel. Johnson & Johnson v. Karl*, 647 S.E.2d at 908  
n.14. The FDA Modernization Act of 1997, 21 U.S.C. §301

(1997) *et seq.*, led to another increase in DTC advertising of prescription drugs.

### **(3) Cialis is a Recreational Life-Style Drug**

Until recently ED had always been considered a normal, even welcome, sign of healthy aging.<sup>27/</sup> Treating ED as a disease would have been considered antithetical to the social norm of retired men devoting themselves to other interests, such as gardening or stamp collecting, in the natural progression onto the next sequential stage of life.<sup>28/</sup>

ED wasn't coded as a disease until as recently as 2016 under the ICD-10<sup>29/</sup> convention as "N52.9 - Male erectile dysfunction, unspecified". Prior to 2016, before the

---

<sup>27/</sup> Wentzell, Labuski, *Role of Medical Anthropology in Understanding Cultural Differences in Sexuality*, 2020, Cham: Springer International Publishing, 23-35.

<sup>28/</sup> *Id.*

<sup>29/</sup> International Classification of Diseases (ICD) is a diagnostic tool maintained by the World Health Organization (WHO) used for statistical, epidemiological and health management purposes. Its most recent manifestation, the ICD-10, in use since 1994, will be replaced by the ICD-11 on January 1, 2022.

pharmaceutical industry convinced everyone that ED is a disease, there was the non-billable code of 607.84 under the general category as “Impotence of Organic Origin.”

Cialis does not save anyone’s life nor does it relieve pain.

It does not cure cancer and does not restore kidney function.

Cialis is not the kind of drug anticipated in Restatement (Second) of Torts § 402A (1965):

There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs.

*Id.* Comment K.

The “Restatement (Second)” offers the example of Pasteur’s rabies vaccine “which not uncommonly leads to very serious and damaging consequences when it is injected.”

Because the side-effects of the vaccine are an acceptable alternative to a painful death, on balance the vaccine is preferable despite the side-effects.

Since the disease itself invariably leads to a dreadful death, both the marketing and the use of

the vaccine are fully justified, notwithstanding the unavoidable high degree of risk which they involve.

Ibid.

Under Washington law, in order to fit the legal definition of “unavoidably unsafe,” and thus be eligible for the LID as a defense, a drug must meet all four of the criteria listed under Comment k of Section 402A of Restatement (Second) of Torts, adopted by this Court in *Terhune v. A. H. Robins Co.*, 90 Wash.2d 9, 577 P.2d 975 (1978):

(1) A showing that the product is incapable of being made safe for its intended and ordinary use; (2) That the benefits of the product justify its marketing and use despite the unavoidable risks; (3) That the product is properly prepared and marketed, and (4) That the product is accompanied by proper directions and warnings.

Cialis fails on at least two criteria of Comment k: Cialis is a recreational “life-style” drug, the kind mentioned by the Supreme Court of New Jersey:

[W]hen one considers that many of these "life-style" drugs or elective treatments cause significant side effects without any curative effect, increased consumer protection becomes imperative, because these drugs are, by definition, not medically necessary.

*Perez v. Weyth Labs Inc., supra*, 734 A.2d. at 1257 (quotation marks in original). The benefits of Cialis, as a 100% recreational "life-style" drug,<sup>30/</sup> do not justify its risk of ICH. Moreover, as observed by four neurology professors reporting in the journal Missouri Medicine:

FDA warns against possible cardiovascular adverse reactions, hearing loss, hypotension, and priapism, *however does not warn that ICH may be [sic] possible side effect.*

Lucchese, Dhaliwal, Kaur, Qi; *A Case of Recurrent Lobar Intracerebral Hemorrhage in the Setting of Phosphodiesterase-5 Inhibitor Use*, Missouri Medicine, 2019 116:5. (Appendix 27-30)(emphasis added).

---

<sup>30/</sup> There are adequate substitutes for the other FDA approved uses for Cialis (see note 14 at page 7): a variety of alpha blockers can treat BPH, and endothelin receptor antagonists can treat PAH.

Thus Cialis does not fit the category of drugs embodied within the scope of Comment k to qualify as “unavoidably unsafe.” In any event, assuming that DTC advertising was not involved, Defendant is nevertheless ineligible for application of the LID as a defense. Cialis does not fit the exception provided by Comment k, of Section 402A of the Restatement (Second) of Torts.

## **B. Why the Learned Intermediary Doctrine Must Be Re-examined**

### **(1) The LID Encourages Irresponsible Behavior**

Many courts and commentators have viewed commerce as a flowing “stream,”<sup>31/</sup> a metaphor to represent the process

---

<sup>31/</sup> The concept perhaps first began with Associate Justice Oliver Wendell Holmes, Jr. writing for a unanimous court, as he metaphorically viewed commerce in the abstract as a “current” to describe the movement of a product through interstate commerce, *Swift & Co. v. United States*, 196 U.S. 375, 399, 25 S.Ct. 276, 49 L.Ed. 518 (1905)(a purchase of cattle at the local stockyard affects the interstate continuum of trade, thereby invoking the Sherman Act to break-up the horizontal monopoly of the “Beef Trust” in accordance with the goals of the T. Roosevelt Administration; “the current thus existing is a current of commerce among the States”) as did Chief Justice (and former president) William Howard Taft nearly two decades later in *Stafford v. Wallace*, 258 U.S. 495, 516, 42

whereby a product is manufactured, then passed onto a broker, then the wholesaler, then retailer, and eventually to the ultimate consumer of the product. “Stream of commerce” is an apt description befitting a time predating the automobile.

Plaintiffs, however, suggest that commerce is more aptly described as a multilane superhighway, something unknown in 1905 because there were no automobiles then.

On the “highway” of commerce there are varied lanes separated by the repercussions of the buying decisions involved. There are lanes reserved for impulse buying, such as a new flavor of chewing gum, where the time required for the decision to purchase can be measured in milliseconds; retailers call such purchases “impulse buying” (those items that store owners move close to the cash register) where the purchase ramifications are *de minimus*.

---

S.Ct. 397, 66 L.Ed. 735 (1922)(“The stockyards and the sales are necessary factors in the middle of this current of commerce”).

Conversely, there is a lane for products that consumers may require years to decide whether to purchase. These products include homes, vehicles, cosmetic surgery, etc. The ramifications are long term and sometimes permanent.

The prescription drug manufactured by the Defendant, Cialis, should travel the lane closer to the latter example where purchases require much deliberation. Unfortunately there would be fewer sales of Cialis if consumers deliberated on whether to purchase a “life-style” drug that carried a possible side-effect of ICH. Thus Defendant “changed lanes” <sup>32/</sup> to be closer to the lane reserved for impulsive sales (which explains the bikinis, see note 19 at page 10).

Prescription drugs have twenty (20) years of patent protection, which provide only a small window of opportunity where drug manufactures can earn maximum profits without competition in the marketplace from generic drug makers.

---

<sup>32/</sup> Our young people like to remind others, those with whom they disagree (sometimes their parents), to “stay in your own lane” in order to achieve a desired result.

This is Defendant's annual gross revenue earned from sales of Cialis from the time of FDA approval to the present: <sup>33/</sup>

2003	0.203 Billion
2004	0.552 Billion
2005	0.747 Billion
2006	0.971 Billion
2007	1.144 Billion
2008	1.444 Billion
2009	1.559 Billion
2010	1.699 Billion
2011	1.876 Billion
2012	1.927 Billion
2013	2.159 Billion
2014	2.291 Billion
2015	2.311 Billion
2016	2.472 Billion
2017	2.323 Billion
2018	1.853 Billion
2019	0.891 Billion
2020	0.607 Billion

Notice the peak from 2016 to the gradual drop in revenue as the Cialis patent begins to expire. Moreover, the main Cialis competitor, Viagra, lost its patent five years earlier, thus permitting a cheaper generic version of the PDE<sub>5</sub> inhibitor into the marketplace to drive prices down.

---

<sup>33/</sup> <https://investor.lilly.com/financial-information/annual-reports> (last visited September 10, 2021).

One of the many unintended consequences of the LID is that it removes an important incentive for powerful drug manufacturing corporations to behave responsibly.

The Federal Government reported in 2006 that the pharmaceutical industry had spent more on DTC advertising than it had spent on research and development. <sup>34/</sup>

Plaintiffs have demonstrated that Defendant (and other drug manufacturers) withheld knowledge of the dangerous side-effect of ICH when taking PDE<sub>5</sub> inhibitors and did so deliberately to generate maximum revenue and worry later about paying damages.

As was observed by a California Appellate Court:

[T]he manufacturer may find it more profitable to treat compensatory damages as a part of the cost of doing business rather than to remedy the defect.

*Grimshaw v. Ford Motor Co.* 119 Cal. App.3d 757, 174 Cal. Rptr. 348 (1981).

---

<sup>34/</sup> Government Accounting Office (GAO)- 07-54 Prescription Drugs: Improvements Needed in FDA'S Oversight of Direct-To-Consumer Advertising 5, 12 (Nov. 2006).

Perhaps the Defendant and other manufacturers of PDE<sub>5</sub> inhibitors thought it more profitable to keep quiet about ICH <sup>35/</sup> and “treat compensatory damages as a part of the cost of doing business.” *Grimshaw.*

During the time Defendant enjoyed the privilege of the LID, it ventured into a different lane on the highway of commerce: the lane reserved for safe (which Cialis certainly is not) products requiring little deliberation to purchase, while enjoying the windfall profits beneath the protective wing of the LID.

Defendant and other manufactures could not have generated such windfall profits marketing PDE<sub>5</sub> inhibitors if it warned the public and physicians about the side-effect of ICH.

---

<sup>35/</sup> Defendant stated as much in its 2017 financial reporting: “Because of the nature of pharmaceutical products, we could become subject to large numbers of product liability claims for these or other products in the future, which could require substantial expenditures to resolve and, if involving marketed products, *could adversely affect sales of the product.*” *Eli Lilly and Company 2003 Annual Report*, at page F20 (italics ours). <https://investor.lilly.com/financial-information/annual-reports> (last visited September 10, 2021).

Had the LID not been available as a carte blanche for the Defendant to evade the general requirement to warn the public of dangerous side-effects, its DTC advertising would have included a warning against a possible ICH when ingesting Cialis. With the LID in force Defendant gives little or no regard to the potential legal consequences of causing debilitating drug injuries with its refusal to warn about the danger of ICH, so it yet continues to market Cialis with impunity.

In the case of PDE<sub>5</sub> inhibitors, the LID hinders the patient-doctor relationship, encourages patients to choose drug-based solutions over lifestyle-based ones, it reduces the amount spent on research and development, and increases spending on drugs without a corresponding health benefit. <sup>36/</sup>

//

//

---

<sup>36/</sup> Angell, *Relationships with the Drug Industry: Keep at Arm's Length*, 2009, 338 Brit. Med. J. b222 (2009).

## **(2) A DTC Exception to LID Would Not Create a Chilling Effect**

The worst kept secret among the more fierce advocates of the LID is the fear that important drug discoveries will no longer be forthcoming if the pharmaceutical industry loses the financial incentive or freedom to experiment. Those advocates call this a “chilling effect” on the Pharmaceutical Industry’s ability to discover new drug therapies.

Some commentators (that might possibly be on the pharmaceutical industry payroll) have sung like troubadours of the virtues of the LID and lament over the possibility of a world without new drug research if courts take one step toward limiting the LID for drug companies that utilize DTC advertising.<sup>37/</sup>

---

<sup>37/</sup> Cf. Rosok, *Direct-to- Consumer Advertising of Prescription Drugs: After a Decade of Speculation, Courts Consider Another Exception to the Learned Intermediary Rule*, (2000), 24 Seattle U. L. Rev. 629; Allen, *Medicine Goes Madison Avenue: An Evaluation of the Effect of Direct-to-Consumer Pharmaceutical Advertising on the Learned Intermediary Doctrine*, (1997), 20 Campbell L. Rev. 113.

Plaintiffs submit that as long as capitalism remains alive and well in this country, the profit motive will continue to generate entrepreneurship, even within the pharmaceutical industry. "The profit motive is the engine that ensures the progress of science." *American Geophysical Union v. Texaco Inc.*, 802 F. Supp. 1, 27 (S.D.N.Y. 1992), aff'd, 60 F.3d 913 (2nd Cir. 1994).

### **C. This Case Demands Authorizing of Punitive Damages**

Because Defendant has acted to withhold disclosure that Cialis can cause ICH, this Court should determine that the actions of Defendant were so egregious as to warrant punitive damages.

The United States District Court has broadened the scope of the certified question to include:

. . . consideration of any other issues that it determines are relevant. Moreover, the Washington Supreme Court may, in its discretion, reformulate the question in whatever manner it finds most appropriate. See *Affiliated FM Ins. Co.*

v. *LTK Consulting Servs. Inc.*, 556 F.3d 920, 922 (9th Cir. 2009).

Order of July 6, 2021 (Dkt. No. 28).

## VI. CONCLUSION

Mapping of the complete human genome marked an important milestone in medical discovery.<sup>38/</sup> As a result of that achievement, drugs can someday be engineered to fit each individual according to his or her own genetic profile.

As we prepare to cross that threshold we need now, more than ever, a robust pharmaceutical industry to meet the challenging demands of the twenty-first century. But that need does not override our need for the pharmaceutical industry to behave responsibly.

By limiting the reach of the learned intermediary doctrine, this Court will put drug manufacturers on notice, that those doing business in the State of Washington that “change

---

<sup>38/</sup> <https://www.ncbi.nlm.nih.gov> (last visited September 10, 2021).

lanes” in order to increase revenue using DTC marketing, will no longer enjoy the protection of the LID to market their product directly to the public, that they must disclose all and every dangerous side effects at the time of their marketing.

DATED: This 10th day of September, 2021.

Respectfully Submitted,

/s/ David J. Dearinger  
David J. Dearinger, Plaintiff, *pro se*  
10218 38th Pl SE  
Lake Stevens, WA 98258-5738  
(425) 220-3690 cell  
[daviddearinger@comcast.net](mailto:daviddearinger@comcast.net)

/s/ Ganna P. Dearinger  
Ganna P. Dearinger, Plaintiff, *pro se*  
10218 38th Pl SE  
Lake Stevens, WA 98258-5738  
(425) 220-3691 cell

**CERTIFICATE OF COMPLIANCE**

Pursuant to RAP 18.17(b) Plaintiffs hereby certify that  
this document contains 6,736 words, exclusive of the title page,  
table of contents, table of authorities, signature blocks,  
certificate of compliance, certificate of service, and appendix.

DATED: This 10th day of September, 2021.

Respectfully Submitted,

/s/ David J. Dearinger  
\_\_\_\_\_  
David J. Dearinger, Plaintiff, *pro se*  
10218 38th Pl SE  
Lake Stevens, WA 98258-5738  
(425) 220-3690 cell  
[daviddearinger@comcast.net](mailto:daviddearinger@comcast.net)

**CERTIFICATE OF SERVICE**

I certify that, on this day, I sent a copy of this document via e-mail (by agreement under RAP 18.5(a) and CR 5(b)(7)) to the attorneys for the Respondent:

Anne M. Talcott, WSBA #26886  
Email: atalcott@schwabe.com  
1211 SW 5th Avenue, Suite 1900  
Portland, OR 97204  
and  
Kainui M. Smith, WSBA #53877  
Email: ksmith@schwabe.com  
1420 5th Avenue, Suite 3400  
Seattle, WA 98101

I declare under penalty of perjury under the laws of the State of Washington that the foregoing is true and correct.

DATED: This 10th day of September, 2021 at Lake Stevens, Washington.

/s/ David J. Dearinger  
\_\_\_\_\_  
David J. Dearinger, Plaintiff, *pro se*  
10218 38th Pl SE  
Lake Stevens, WA 98258-5738  
(425) 220-3690 cell  
[daviddearinger@comcast.net](mailto:daviddearinger@comcast.net)

# **APPENDIX**

Roberto Monastero  
Carmela Pipia  
Lawrence K. C. Camarda  
Rosolino Camarda

## Intracerebral haemorrhage associated with sildenafil citrate

Received: 15 February 2000  
Received in revised form: 8 June 2000  
Accepted: 25 July 2000

Sirs: Sildenafil is an orally active, potent and selective inhibitor of phosphodiesterase type 5 (PDE-5), an important regulator of cyclic guanosine monophosphate (cGMP) in the human corpus cavernosum which has recently been introduced for the treatment of erectile dysfunction. Sildenafil acts by increasing the concentration of cGMP in the corpus cavernosum smooth muscle cells leading to muscle relaxation, vasodilatation and penile erection [1]. Adverse effects include headache, visual and retinal disturbances, dizziness and a pupil-sparing third nerve palsy [2, 5, 7]. We report a patient who developed intracerebral haemorrhage (ICH) after sildenafil consumption.

A 67-year-old dentist was referred to our clinic in a confusional state together with speech, numeracy and memory disturbances. From the history it appeared that 5 days before admission, approximately 30 minutes after the ingestion of one tablet of sildenafil 25 mg, the patient complained of headache, confusion and nervousness without improvement in sexual function. One hour after the ingestion of the first tablet the patient took another 25 mg tablet, again without sexual intercourse. According to his wife, these symptoms increased together with language difficulty. The patient was

admitted to our department 5 days later. He had never used sildenafil before. The history revealed no arterial hypertension or migraine or haemostatic risk factors (e.g. use of anticoagulants or antiplatelet drugs, thrombolytic treatment), history of head trauma, hypercholesterolaemia, diabetes mellitus, pre-existing cardiovascular disease or cerebrovascular episodes such as stroke or transient ischaemic attacks. There was no family history of cerebral arteriovenous malformation, intracerebral aneurysms, or intracerebral haemorrhages. He had a 40-year history of tobacco abuse (approximately 15 cigarettes a day) and denied regular alcohol intake. He took no other medications.

On admission his blood pressure was 140/90 mmHg and pulse was 68/min. Neurological examination showed a right superior homonymous quadrantanopia and psychiatric examination a dysphoretic mood. Ophthalmoscopic examination was normal. Neuropsychological testing revealed a moderate impairment of comprehen-

sion, naming, reading and writing with a relative sparing of repetition, acalculia, finger agnosia, colour anomia, and discrete involvement of episodic memory. Routine blood examination, platelet count and coagulation factors were normal, as well as electrocardiography, and colour-coded duplex sonography of extracranial vessels. Transcranial colour-coded duplex sonography revealed a sharply demarcated hyperechogenic area confined to the left temporal lobe. Two days after admission basal and gadolinium-enhanced T1-/T2-weighted cerebral magnetic resonance imaging revealed a large left temporal subcortical haemorrhage with moderate surrounding oedema (see Fig. 1). Although the chance of finding a clinically relevant vascular lesion in a patient 67 years old is very small, we would have liked to have performed cerebral angiography. However, the patient's wife, informed of the potential risk of cerebral angiography, refused her consent due to her husband's advanced age and the presence of a deep lobar ICH. The patient was treated with intravenous bolus of 1 g/kg mannitol, followed by 0.5 g/kg every 4 h for 7 days. He was discharged 5 days later with mild comprehension, reading, writing and episodic memory deficits, moderate acalculia, finger agnosia and colour anomia. The field defect was still present.

The close temporal relationship between sildenafil ingestion and onset of the neurological symptoms due to the ICH in a patient without a history of cerebrovascular accident or obvious risk factors for ICH suggest that sildenafil was causally related to the ICH. Smoking is currently not considered a primary risk factor for ICH [4, 6]. Since the symptoms started before any attempt at sexual intercourse, sexual exertion cannot be regarded



**Fig. 1** Axial T1-weighted gadolinium-enhanced magnetic resonance imaging shows hyperintense signal lesion confined subcortically to the left temporal lobe

as the precipitating factor. Common adverse effects of sildenafil, such as flushing, headache and nasal congestion, indicate that vasodilatation is not confined to the corpus cavernosum [5]. On the other hand, the reported occurrence of acute myocardial infarction suggests that the drug may also act by redistributing the arterial blood flow, in turn reducing vessel perfusion [3]. The reported occurrence of headache, dizziness, visual disturbances, retinal dysfunction and a pupil-sparing third nerve palsy suggest that sildenafil also affects brain microvasculature regulation [2, 5, 7]. Recently, Ballard et al. [1] in an in vitro study have shown that sildenafil, in addition to a selective action on PDE-5, may also act on other two PDEs (i.e. PDE-1 and PDE-2) which are involved in the control of cerebral vasculature. In our case a particular susceptibility to the drug may have led to an abnormal, persistent vasodilatation of cerebral arteries and to an abnormal redistribution of arterial brain blood flow. Furthermore, our patient took a second 25 mg tablet within 1 h of ingestion of the first one, despite the manufacturer's advice suggesting

that the initial sildenafil dose in the elderly should be 25 mg. These factors may have increased the risk of a bleeding phenomenon in a subject with a senescent cerebral circulation. As cerebral angiography was not carried out in our patient, it remains unclear to what extent pre-existing cerebral microvascular disease contributed to the onset of ICH. However, although less accurate than cerebral angiography, brain magnetic resonance imaging and transcranial colour-coded duplex sonography did not show any cerebral malformations.

In conclusion, our case and the frequency of reported vascular adverse effects suggest that sildenafil should be used with caution in the elderly, especially when the minimum dose recommended by the manufacturer does not improve sexual function to first-time users. Longitudinal pharmacological studies in an elderly population are necessary to clarify this issue.

**Acknowledgements** R.M. was supported by a fellowship in Neuropsychology from Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST). This work was supported by MURST grants to R.C. The authors are grateful to Mrs. Gay Marks for help in the English revision of the manuscript.

## References

- Ballard SA, Gingell CJ, Tang K, Turner LA, Price ME, Naylor AM (1998) Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes. *J Urol* 159:2164–2171
- Donahue SP, Taylor RJ (1998) Pupil-sparing third nerve palsy associated with sildenafil citrate (Viagra). *Am J Ophthalmol* 126:476–477
- Feeenstra J, van Drie-Pierik RJ, Laclé CF, Stricker BH (1998) Acute myocardial infarction associated with sildenafil. *Lancet* 352:957–958
- Juvela S, Hillbom M, Palomaki H (1995) Risk factors for spontaneous intracerebral hemorrhage. *Stroke* 26:1558–1564
- Morales A, Gingell C, Collins M, Wicker PA, Osterloh IH (1998) Clinical safety of oral sildenafil citrate (Viagra) in the treatment of erectile dysfunction. *Int J Impot Res* 10:69–73
- Thrift AG, McNeil JJ, Forbes A, Donnan GA (1996) Risk factors for cerebral hemorrhage in the era of well-controlled hypertension. Melbourne Risk Factors Study (MERFS) Group. *Stroke* 27:2020–2025
- Vobig MA, Klotz T, Staak M, Bartz-Schmidt KU, Engelmann U, Walter P (1999) Retinal side-effects of sildenafil. *Lancet* 353:375

R. Monastero · C. Pipia · L. K. C. Camarda ·  
R. Camarda (✉)  
Second Department of Neurology  
Institute of Neuropsychiatry  
University of Palermo  
Via La Loggia 1  
90129 Palermo, Italy  
Tel.: +39-91-6555112/20  
Fax: +39-91-6555113  
e-mail: rcamarda@neuro.unipa.it

# Coital Hemorrhage of an Arteriovenous Malformation after Premedication with Tadalafil (Cialis)

Thomas D.L. Steeves, MD,\* Lyell K. Jones, MD,\* Robert D. Ecker, MD,†  
and Edward M. Manno, MD\*

---

Phosphodiesterase type 5 (PDE 5) inhibitors are widely used in the treatment of erectile dysfunction. However, the results on the cerebral vasculature are unknown. Several cases of intraparenchymal hemorrhage in the setting of PDE 5 inhibitor use have been reported. The effect of these agents on the risk of arteriovenous malformation (AVM) hemorrhage is speculative. This report illustrates a possible association between tadalafil (Cialis, Lilly ICOS, Indianapolis, IN), a new long-acting PDE 5 inhibitor, and AVM hemorrhage during coitus. A 59-year-old male suffered a coital intraparenchymal hemorrhage after premedication with tadalafil. Angiography and magnetic resonance imaging demonstrated an underlying right temporoparietal AVM. The AVM was excised, and the patient made an uneventful recovery. AVMs are felt to be dynamic lesions that evolve in response to changes in blood flow. Repeated use of PDE 5 inhibitors could induce changes in an AVM that would make it more likely to hemorrhage, particularly in the setting of additional stress from coitus and elevated blood pressure. The potential for risk of devastating neurovascular complications related to PDE 5 inhibitors should be monitored. **Key Words:** Coital hemorrhage—arteriovenous malformation—tadalafil.

© 2005 by National Stroke Association

---

More than 100 million men worldwide suffer from erectile dysfunction. In 1998, sildenafil citrate (Viagra), the first oral phosphodiesterase type 5 (PDE 5) inhibitor for the treatment of this condition, was approved. Since its introduction, sildenafil has been prescribed to more than 15 million men worldwide.<sup>1</sup> Its sales approach \$US 2 billion annually in a market whose value is expected to reach \$US 6 billion by the end of the decade.<sup>2</sup> In 2003, the FDA approved 2 new PDE 5 inhibitors: vardenafil (Levitra, Bayer, Pittsburgh, PA), distinguished from sildenafil by greater biochemical potency, and tadalafil (Cialis, Lilly ICOS), which is unique for its prolonged half-life and extended window of efficacy.

---

From the Departments of \*Neurology and †Neurosurgery, Mayo Clinic College of Medicine, Rochester, Minnesota.

Received March 10, 2005; accepted March 17, 2005.

Address reprint requests to Edward M. Manno, MD, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905. E-mail: manno.edward@mayo.edu.

1052-3057/\$—see front matter

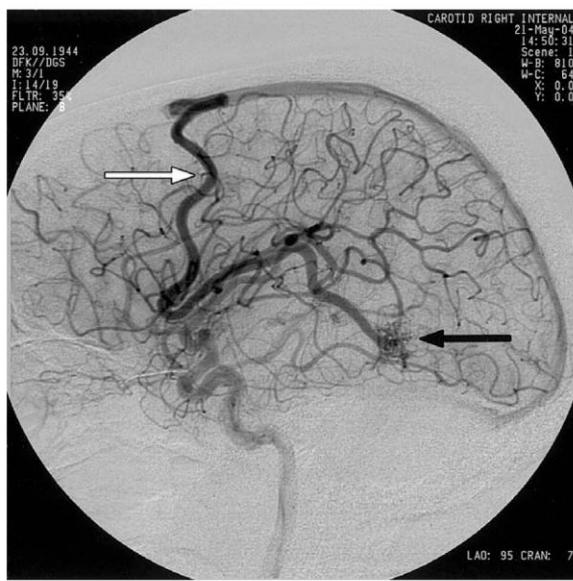
© 2005 by National Stroke Association

doi:10.1016/j.jstrokecerebrovasdis.2005.03.005

PDE 5 is an isoenzyme of a family of cGMP hydrolyzing enzymes. It is located in vascular smooth muscle cells of the penile corpus cavernosum, as well as in various other human tissues, including the brain and cerebral arteries. In the corpus cavernosum, inhibitors of this enzyme permit cGMP to accumulate after its production in response to sexual arousal, which in turn relaxes the smooth muscle of the penile vasculature to allow vaso-dilatation and erection. The effect of these agents on the cerebral vasculature is unclear. Although PDE 5 inhibitors are not known to confer an increased risk of central nervous system hemorrhage, several cases of intraparenchymal hemorrhage associated with their use have been documented. Here we describe a case of coital hemorrhage of an arteriovenous malformation (AVM) after premedication with tadalafil.

## Case Report

A 59-year-old right-handed man with a history of hypertension and erectile dysfunction presented to an outside emergency room after developing severe right-



**Figure 1.** Appearance of AVM on angiogram. The right intracranial artery injection demonstrates a small AVM located in the superficial aspect of the posterior right temporal lobe (dark arrow) fed by a small branch of the angular artery. The arterial phase demonstrates a single superficial draining vein (white arrow) ascending laterally to empty into the superior sagittal sinus.

sided headache during intercourse. Two months before this incident, his primary care physician had prescribed tadalafil for erectile dysfunction, and the patient had used this medication several times with favorable results and no adverse effects. On this occasion he had taken 10 mg of tadalafil 2 hours before intercourse. He experienced no neurologic symptoms until intercourse, at which time he had an abrupt onset of a 9/10 right-sided posterior parietal headache. He discontinued his activity and took an aspirin as well as fexofenadine (Allegra, Aventis Pharmaceuticals, Bridgewater, NJ) for nasal congestion. He sought medical attention when his headache did not improve after approximately 1 hour.

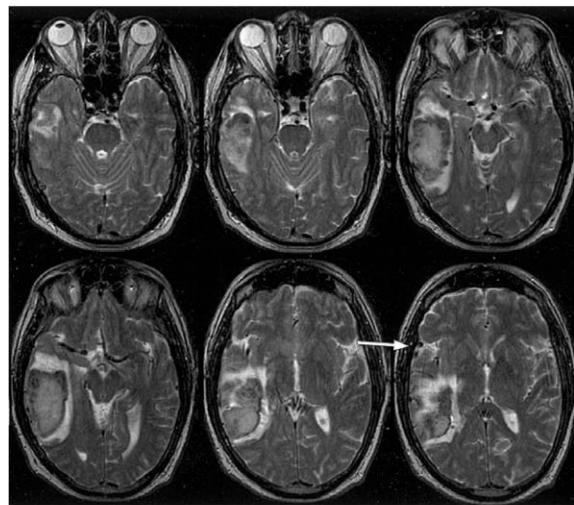
On initial examination at his local hospital, the patient was found to be neurologically intact. However, a head computed tomography scan revealed an acute 3.5 cm × 4.5 cm × 6.5 cm bleed in the right temporoparietal area. The patient was transferred to the neurologic intensive care unit at our institution for further management. On arrival, his only neurologic deficits were a mild left pronator drift and an inconsistent visual field exam by confrontation that suggested a possible left homonymous hemianopsia.

Cerebral angiography (Fig 1) demonstrated a small AVM located in the superficial aspect of the posterior right temporal lobe fed by a branch of the angular artery. A single superficial draining vein ascended laterally to empty into the superior sagittal sinus. Magnetic resonance imaging (MRI) (Fig 2) showed a 4.2 cm × 4.8 cm ×

8.2 cm hyperacute intraparenchymal hemorrhage centered within the right temporal lobe and extending into the most anterior aspect of the right parietal lobe. Multiple enlarged vessels were seen in the sylvian fissure, as well as the previously noted superficial draining vein to the superior sagittal sinus. Formal visual field testing confirmed a complete left hemianopsia. The patient was taken to surgery, and the AVM was excised. He had an uneventful postoperative course and was discharged home with a resolving left-sided hemianopsia as his only remaining neurologic deficit.

## Discussion

A number of adverse neurologic events are associated with sexual intercourse. Benign coital headache, vertebral and carotid artery dissection, and subarachnoid hemorrhage during coitus are all well known to neurosurgeons and neurologists. However, documentation of these events has been limited. Finelli<sup>3</sup> reported a case of hemorrhage of a probable cavernous malformation during sexual intercourse in a hypertensive patient. More recently, several cases of intraparenchymal hemorrhage associated with sildenafil citrate, both with and without intercourse, have been described. Monastero et al<sup>4</sup> reported a lobar hemorrhage associated with sildenafil but without intercourse. Buxton et al<sup>5</sup> described a lobar hemorrhage after intercourse and premedication with sildenafil that ultimately resulted in the patient's death. Most recently, Marti and Masso<sup>6</sup> described a midbrain hemorrhage occurring after premedication with sildenafil and intercourse, although the exact onset of symptoms in



**Figure 2.** T2-weighted MRI demonstrating a large 4.2 cm × 4.8 cm × 8.2 cm hyperacute intraparenchymal hemorrhage centered within the right temporal lobe and extending into the most anterior aspect of the right parietal lobe. Multiple enlarged vessels are seen in the sylvian fissure as well as in the large superficial draining vein (white arrow) to the superior sagittal sinus.

relation to these events was not described. To our knowledge, no coital hemorrhage of an AVM in association with tadalafil, has yet been reported.

Our patient was a 59-year-old man with a history of moderate hypertension and an underlying AVM whose hemorrhage occurred during intercourse and after pre-medication with tadalafil. Given that the hemodynamic determinants of AVM hemorrhage have not been defined, to what extent these factors may have interacted to increase this patient's risk of hemorrhage is open to speculation.

Coitus is well known to have a marked effect on blood pressure in both normal and hypertensive subjects. Continuous intra-arterial blood pressure monitoring in ambulant hypertensive subjects has shown peaks values of up to 300/175 mmHg during intercourse, with a mean of 237/138 for men and 216/127 for women.<sup>7</sup> In this context, it is possible that extreme hypertension alone triggered this man's hemorrhage, but the potential contribution of tadalafil to the presentation, whether directly or even indirectly by permitting him to engage in intercourse, also should be considered.

The adverse effect profile of all PDE 5 inhibitors is similar and includes headache, facial flushing, gastroesophageal reflux, nasal congestion, and visual disturbances. Tadalafil is also associated with myalgias and back pain, although the mechanism behind these symptoms is unclear. The effects of these agents on the intracranial vasculature are still being elucidated. Tadalafil has greater selectivity than sildenafil for PDE 5 compared with the other PDE isoenzymes.<sup>1-6,8</sup> But Kruuse et al<sup>9</sup> have shown that PDE 5 is present in the cerebral arteries of both rodents and humans, and that in vitro rodent cerebral arteries dilate in response to PDE inhibitors. However, in a more recent human study evaluating the effects of sildenafil on cerebral blood flow, Kruuse et al<sup>10</sup> detected no changes in middle cerebral artery diameter as measured with Doppler ultrasound and no change in cerebral blood flow as measured with single-photon emission computed tomography.

The potential effects of the PDE inhibitors on AVM likewise have not been established; however, increased blood flow is known to produce progressive vessel changes in experimental models of AVMs. Tears in the internal elastic lamina of the afferent artery occur after 2-5 days of high flow, and further changes progress to involve all layers of the vessel to the point where it can no

longer be identified as an artery or a vein.<sup>11</sup> It remains possible that repeated use of PDEs, particularly those with prolonged half-lives such as tadalafil, could induce changes in an AVM that would make it more likely to hemorrhage when additional stresses from exertion and elevated blood pressure were placed on it. This is precisely the scenario that would be repeated time and again with the chronic use of tadalafil in sexual intercourse. Given the increasing popularity of these agents and the potential for their widespread use and abuse as performance enhancers even among relatively young individuals who do not suffer from erectile dysfunction, the risk of devastating neurovascular complication should be monitored.

## References

1. Hopps CV, Mulhall JP. Novel agents for sexual dysfunction. *BJU Int* 2003;92:534-538.
2. Naughton K. Cialis is here. The soft sell. *Newsweek* 2004;143:46-47.
3. Finelli PF. Coital cerebral hemorrhage. *Neurology* 1993; 43:2683-2685.
4. Monastero R, Pipia C, Camarda LK, et al. Intracerebral haemorrhage associated with sildenafil citrate. *J Neurol* 2001;248:141-142.
5. Buxton N, Flannery T, Wild D, et al. Sildenafil (Viagra)-induced spontaneous intracerebral haemorrhage. *Br J Neurosurg* 2001;15:347-349.
6. Marti I, Marti Masso JF. Hemiballism due to sildenafil use. *Neurology* 2004;63:534.
7. Mann S, Craig MW, Gould BA, et al. Coital blood pressure in hypertensives. *Cephalgia, syncope, and the effects of beta-blockade*. *Br Heart J* 1982;47:84-89.
8. Daugan A, Grondin P, Ruault C, et al. The discovery of tadalafil: a novel and highly selective PDE5 inhibitor. 2: 2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione analogues. *J Med Chem* 2003;46:4533-4542.
9. Kruuse C, Rybalkin SD, Khurana TS, et al. The role of cGMP hydrolysing phosphodiesterases 1 and 5 in cerebral artery dilatation. *Eur J Pharmacol* 2001;420:55-65.
10. Kruuse C, Thomsen LL, Jacobsen TB, et al. The phosphodiesterase 5 inhibitor sildenafil has no effect on cerebral blood flow or blood velocity, but nevertheless induces headache in healthy subjects. *J Cereb Blood Flow Metab* 2002;22:1124-1131.
11. Pile-Spellman JM, Baker KF, Liszczak TM, et al. High-flow angiopathy: cerebral blood vessel changes in experimental chronic arteriovenous fistula. *AJNR Am J Neuroradiol* 1986;7:811-815.

**Sudden deafness from stroke**

**To the Editor:** I was fascinated by the report by Leussink et al.<sup>1</sup> and how their patient, following a stroke, became suddenly and totally deaf, but had no realization that this was the case. This singular unconsciousness of a deficit is reminiscent of Anton syndrome, in which patients with cortical blindness may not only fail to realize that they are blind, but strenuously maintain that they can see perfectly. When, as inevitably happens, they blunder into objects, they immediately explain such accidents by confabulations ("the furniture has been moved," "the light is bad"). One is tempted to see Leussink and colleagues' case as an example of auditory Anton syndrome. It would be valuable to have more information about this patient. How, for example, did she explain her inability to understand people's speech? Did she confabulate reasons for this, like someone with Anton syndrome? And what, in retrospect, did she make of her strange week of cortical deafness after she had recovered her hearing?

Oliver W. Sacks, MD, New York, NY

**Reply from the Authors:** We feel honored and thank Dr. Sacks for his interest in our case<sup>1</sup> and his suggestion that our patient could have had Anton syndrome of the auditory system. With the publication space limitation, we could not mention all the details.

At first presentation, the prevailing impression that our patient gave was that of a perplexity and helplessness. She realized the effort that her family and medical staff made to communicate with her. In the first hours, she just seemed to realize that there was something wrong with her without being able to address the problem.

After some hours, noticing lip movements in these people, she would look at the person saying "I cannot hear you," but thereby

did not fully realize that this was part of the more general problem of not being able to hear at all.

While under investigation for auditory brainstem potentials, she would take off the headphones and look at them as if to say "What is this for?" or "What do you expect me to do with it?" She would then stand up from the examination chair and walk away. Concurrently, there was additional difficulty in communication, which we later formally established as a moderate fluent Wernicke type of aphasia. In this context, she would later repeat part of the sentences said to her (always with a question tone as if she was still uncertain of what she had grasped). On dictation, she much preferred to write down the end of sentences and missed the beginning as if the auditory system (or verbal understanding) needed to be slowly tuned up.

The condition substantially improved within 24 hours and subsequently continued to improve. After a few days she told people who set out to communicate with her that she could not hear well. Her premorbid below average level of intelligence probably did not permit her to carefully reflect and communicate the more complex nature of her initial problem. We have no recollection of her interpretation of the initial type of disturbance.

From all these features, we firmly believe that the patient at least initially had a cortical dysfunction that went beyond simple hearing loss. However, with aphasia interfering we are not certain that there was substantial anosognosia associated with it.

Markus Naumann, MD, Augsburg, Germany; Karlheinz Reiners, Würzburg, Germany

Copyright © 2006 by AAN Enterprises, Inc.

**Reference**

- Leussink V, Andermann P, Reiners K, Shehata-Dieler W, Günther-Lengsfeld T, Naumann M. Sudden deafness from stroke. Neurology 2005;64:1817-1818.

**Visual field defect and intracerebral hemorrhage associated with use of vardenafil (Levitra)**

**To the Editor:** McGee et al.<sup>1</sup> report a case of intracerebral hemorrhage (ICH) with vardenafil in a 66-year-old Caucasian male with erectile dysfunction (ED) who had previously used sildenafil. This event has to be viewed within the context of the occurrence of ICH that has been reported with the other currently available phosphodiesterase-5 (PDE-5) inhibitors.

As a point of comparison, McGee et al. cited two reported cases of ICH associated with sildenafil, with a third case reported in 2004.<sup>2</sup> In contrast, there was one case of ICH with tadalafil, which was recently reported.<sup>3</sup> These five reports cite cases of ICH associated with the use of PDE-5 inhibitors.

Worldwide utilization data for sildenafil and tadalafil and US data for vardenafil totals approximately 18.5 million men who have used a PDE-5 inhibitor for ED (according to information from the McGee article, a Medical News Today news brief dated June 3, 2004 available at [www.medicalnewstoday.com/news-search.php?newsid=9046](http://www.medicalnewstoday.com/news-search.php?newsid=9046), and a press release dated February 26, 2004 available at [www.gsk.com](http://www.gsk.com)).

The worldwide incidence of ICH has been estimated to range from 10 to 20 cases per 100,000 population; in the US, the annual incidence of ICH (adjusted for age, sex, and race) is estimated at 15 cases per 100,000 population.<sup>4,5</sup> Used as a point of reference, these numbers show that the risk of ICH among patients using the currently available PDE-5 inhibitors for ED is not considerably different from the general population.

The issue of causality and association of vardenafil with ICH may be difficult to ascertain in this patient in the McGee article because of the following confounders: although rare, ICH has been reported for all 3 PDE-5 inhibitors; the specific doses and duration of therapy with the previously used PDE-5 inhibitor (sildenafil) were not given; although no history of drug use was mentioned, a toxicology screen was not conducted; and a multiplicity of risk factors are involved in the etiology of ICH.<sup>3</sup>

Appropriate use of therapeutic agents includes a benefits-to-risk analysis by the clinician, with a clear and concise explanation given to the patient. The patient should also be informed that ED is often associated with endothelial dysfunction and may be a marker for cardiovascular disease.<sup>6</sup>

Wayne J.G. Hellstrom, MD, New Orleans, LA

**Reply from the Authors:** We appreciate Dr. Hellstrom's response to our article<sup>1</sup> and agree with all of his points. When assessing whether or not a side effect is related to a medication, timing of onset of symptoms in relation to ingestion of drug is important in addition to whether symptoms recur when the patient takes the drug again. Today, serious side effects of medications are difficult to prove since patients are reluctant to rechallenge themselves with a drug they believe was implicated in causing their symptoms. Therefore, we are left with the timing of onset of symptoms to ingestion.

Although we, the authors, are at a loss to hypothesize a mechanism of causation of ICH in our patient, our intention was to alert the medical community to this possible association through publication.

Robert A. Egan, MD, Hall T. McGee, MD, Wayne M. Clark, MD, Portland, OR

Copyright © 2006 by AAN Enterprises, Inc.

**References**

- McGee HT, Egan RA, Clark WM. Visual field defect and intracerebral hemorrhage associated with use of vardenafil (Levitra). Neurology 2005;64:1095-1096.
- Marti I, Marti Masso JF. Hemiballism due to sildenafil use. Neurology 2004;63:534.
- Jones LK. Intracerebral hemorrhage from an arteriovenous malformation after use of tadalafil (Cialis). Presented at: 3rd Annual Meeting of the Neurocritical Care Society; February 27, 2005; Scottsdale, AZ.

January (2 of 2) 2006 NEUROLOGY 66 293

Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

### Reading impairment in the neuronal migration disorder of periventricular nodular heterotopia

**To the Editor:** We read with interest the report by Chang et al.<sup>1</sup> on the association of bilateral periventricular nodular heterotopia with seizures and impaired reading in people with normal intelligence.

We performed extensive neuropsychological testing on a 16-year-old boy with a left periventricular heterotopia and left temporal lobe dysplasia diagnosed by MRI and did not find any evidence of reading disability. Our patient came to evaluation because of academic difficulties. At the time of testing he had focal epilepsy which was well-controlled on lamotrigine. On the Wechsler Intelligence Scale for Children-III Edition, he had a Full Scale intelligence quotient (IQ) of 104, a Verbal IQ of 114, and a Performance IQ of 93. His Processing Speed Index was 64 (1%). On the Gray Oral Reading Test-4, his Reading Quotient was 103 (58% for age) with adequate reading rate, accuracy, frequency, and comprehension for age. On the Luria-Nebraska Neuropsychologic Battery-Form I, none of the 11 clinical scales or 5 ancillary scales were above the critical level of sixty-one. On the Wide Range Achievement Test-Edition III, his reading standard score was 94 at the high school level (34%).

Our patient had normal reading ability. His slow processing speed contributed to his academic difficulty. This case supports the trend described by Chang et al. that patients with fewer

### Excess of serum copper not related to ceruloplasmin in Alzheimer disease

**To the Editor:** I read with interest the article by Squitti et al.<sup>1</sup> I am uncertain of the significance of the non-ceruloplasmin bound copper in the serum of Alzheimer patients. Is it simply a consequence of Alzheimer disease (AD) activity or is directly implicated in the disease process?

AD appears to have free copper unbound by ceruloplasmin in increased amounts. This may have clinical implications since treatment with clioquinol, a metal-protein-attenuating compound which inhibits zinc and copper ions from binding to Abeta and promotes Abeta dissolution, resulted in minimal deterioration of cognitive scores in treated patients compared to substantial deterioration in patients treated with placebo.<sup>2</sup>

Depleted copper levels have been noted to reduce APP production in animals and it is thought the APP regulation of production may represent a target for treatment of AD.<sup>3</sup> The amyloidogenic pathway for Abeta peptides is initiated by BACE1. BACE1 interacts with the copper chaperone for superoxide dismutase-1 and reduces activity of superoxide dismutase through competition for available copper chaperone for superoxide dismutase.<sup>4</sup>

Intracellular copper homeostasis is very regulated, since free cuprous ions react with hydrogen peroxide to yield hydroxyl radical. Copper is imported by plasma membrane transport protein and rapidly binds to intracellular copper chaperone proteins. Amyloid precursor protein may be a copper chaperone protein<sup>5</sup> and defective-free cuprous ions would be available to react with hydroxyl radical, a potent oxidative agent. Copper may interact with multiple mechanisms implicated in AD.

Steven R. Brenner, St. Louis, MO

**Reply from the Authors:** We thank Dr. Brenner for his letter and agree with all the issues raised. Cues to a direct implication of copper in the pathogenetic process leading to AD, rather than this metal being altered as a mere consequence of the disease process, have been given by a number of clinical trials conducted over the past 15 years.<sup>2,6,7</sup>

These trials have provided encouraging results indicating that “metal-protein-attenuating-compounds” can indeed positively modify the natural history of AD. The chelating compound desfer-

rioxamine<sup>6</sup> has demonstrated actual disease slowing effects, while a similar trend has also been shown with the use of clioquinol.<sup>2</sup> However, treatment duration appears to be a fundamental factor, as can it be expected with disease modifying compounds rather than symptomatic approaches.

The administration of clioquinol to AD patients for 36 weeks has provided encouraging results, yet these have been far less important than those obtained by the use of desferrioxamine for 24 months. In addition, a 24-week trial with D-penicillamine<sup>7</sup> showed positive effects in reducing, during the administration phase, the oxidative stress that was present at baseline in AD patients. However, a significant cognitive effect could not be demonstrated in this short observation period due mostly to lack of measurable cognitive deterioration in the placebo group.

We agree with Dr. Brenner that copper is metabolically very finely regulated by the organism and that is precisely why we believe that even a small increase of the serum low molecular weight component can be of a great significance, particularly over a long period of time. When copper is bound to low molecular weight copper compounds, it can be easily exchanged among albumin and small transporter molecules such as peptides or aminoacids.<sup>8</sup> This lability can potentially render copper more toxic and promote oxidative stress, which is significant because these low molecular weight components can easily cross the blood brain barrier.

The putative chaperone role of the Amyloid Precursor Protein (APP) has been shown and may be confirmed by our recent observations (manuscript in preparation) demonstrating a relationship between serum levels of copper unbound to ceruloplasmin and beta amyloid in the cerebrospinal fluid in AD patients.

Rosanna Squitti, PhD, Paolo M. Rossini, MD, Gloria Dal Forno, MD, PhD, Rome, Italy

Copyright © 2006 by AAN Enterprises, Inc.

### References

1. Squitti R, Pasqualetti P, Del Forno G, et al. Excess of serum copper not related to ceruloplasmin in Alzheimer disease. *Neurology* 2005;64: 1040–1046.
2. Ritchie C, Bush A, Mackinnon A, et al. Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting Abeta amyloid deposition and toxicity in Alzheimer disease: a pilot phase 2 clinical trial. *Arch Neurol* 2003;60:1685–1691.

3. Bellingham S, Lahiri D, Maloney B et al. Copper depletion down-regulates expression of the Alzheimer's disease amyloid-beta precursor protein gene. *J Biol Chem* 2004;279:20378–20386.
4. Angeletti B, Waldron K, Freeman K, et al. BACE1 cytoplasmic domain interacts with the copper chaperone for superoxide dismutase-1 and binds copper. *J Biol Chem* 2005;280:17930–17937.
5. Prohaska J, Gybina A. Intracellular copper transport in mammals. *J Nutr* 2004;134:1003–1006.
6. Crapper McLachlan DR, Dalton AJ, Kruck TP, et al. Intramuscular desferrioxamine in patients with Alzheimer's disease. *Lancet* 1991; 337:1304–1308.
7. Squitti R, Rossini PM, Cassetta E, et al. D-penicillamine reduces serum oxidative stress in Alzheimer's disease patients. *Eur J Clin Invest* 2002;32:51–59.
8. Linder MC, Hazegh-Azam M. Copper biochemistry and molecular biology. *Am J Clin Nutr* 1996;63:797S–811S.



#### **WWW.NEUROLOGY.ORG OFFERS IMPORTANT INFORMATION TO PATIENTS AND THEIR FAMILIES**

The *Neurology* Patient Page provides:

- a critical review of ground-breaking discoveries in neurologic research that are written especially for patients and their families
- up-to-date patient information about many neurologic diseases
- links to additional information resources for neurologic patients.

All *Neurology* Patient Page articles can be easily downloaded and printed, and may be reproduced to distribute for educational purposes. Click on the Patient Page icon on the home page ([www.neurology.org](http://www.neurology.org)) for a complete index of Patient Pages.

M. H. Alsan  
N. Bebek  
F. D. Ciftci  
O. Coban  
S. Bahar  
R. Tuncay

### Intracerebral hemorrhage associated with sildenafil use: a case report

Received: 25 January 2007  
Received in revised form: 15 March 2007  
Accepted: 21 March 2007  
Published online: 13 May 2008

Sirs: Intracerebral hemorrhage (ICH) accounts for approximately 10% of all strokes and carries high morbidity and mortality. Causes of nonhypertensive intracerebral hemorrhage are arteriovenous malformations, aneurysms, amyloid angiopathy, coagulopathies and drugs. Drug-induced ICH occurs mostly due to anticoagulants, thrombolytics, sympathomimetics, metamphetamines and cocaine. To our knowledge, there are two previous reported cases about the relationship between sildenafil use and ICH [1,2]. Here we report a case of ICH after a single dose of sildenafil use.

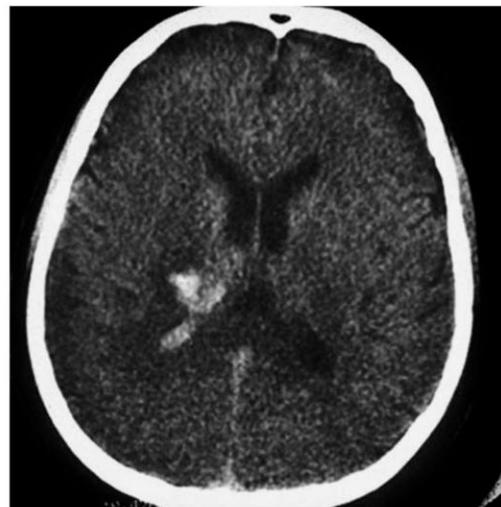
A 62-year-old, right-handed male was admitted with left-sided weakness and numbness. He reported that he had taken 50 mg of sildenafil two hours previously and had noticed numbness and weakness in his left arm and leg an hour after taking the drug. This was the first time he used the drug which was prescribed by a urologist. He indicated that the symptoms devel-

oped before any attempt for sexual intercourse which rules out the possibility of sexual exertion being the precipitating factor. On admission, his blood pressure was 150/90 mmHg and on neurological examination left hemiparesis, hemihypoesthesia, and hemihypalgesia were evident. Cranial CT and MRI showed hemorrhage in the right thalamus, and the posterior limb of the internal capsule (Fig. 1). Intracranial and extracranial MRA were normal. He had a history of mild hypertension but he was not on any antihypertensive treatment. The patient was admitted to the stroke unit and antihypertensive treatment was initiated. Systolic blood pressure was between 120–150 mmHg and diastolic between 80–90 mmHg during his stay. Neurological status improved in one week and at discharge, he only had mild clumsiness of the left hand.

Sildenafil is a selective phosphodiesterase-5 (PDE-5) inhibitor. As a result of PDE-5 inhibition, cyclic

guanosine monophosphate (cGMP) increases in the vascular smooth muscle of corpus cavernosum, leading to muscle relaxation and vasodilation. Several studies have shown that NO-cGMP pathway may be responsible for cerebral vasodilation by similar mechanisms [3]. Recently, Ballard et al. have suggested that sildenafil acts on PDE-1 and PDE-2 which are involved in the control of cerebral vasculature [4]. The increase in the blood flow may have raised the risk of ICH.

Furthermore, it is advised that the initial sildenafil dose in the elderly should be 25 mg. Our patient had taken 50 mg of the drug as the initial dose which might have been another factor increasing the risk of ICH. Sildenafil may be the cause of the intracranial bleeding in our patient although a chance association cannot be ruled out.



**Fig. 1** Hematoma in the right thalamus and the posterior limb of internal capsule

M. H. Alsan · N. Bebek · F. D. Ciftci ·  
O. Coban · S. Bahar · R. Tuncay, MD (✉)  
Dept. of Neurology  
Edip Aktin Stroke Unit  
Istanbul Medical Faculty  
Istanbul University  
34390 Capa, Istanbul, Turkey  
Tel.: +90-21/2621-5623  
E-Mail: tuncay@istanbul.edu.tr

---

**References**

1. Buxton N, Flannery T, Wild D, Bassi S (2001) Sildenafil (Viagra)-induced spontaneous intracerebral haemorrhage. British Journal of Neurosurgery 15:347–349
2. Monastero R, Pipia C, Camarda LKC, Camarda R (2001) Intracerebral haemorrhage associated with sildenafil citrate. J Neurol 248:141–142
3. Mc Hugh J, Cheek DJ (1998) Nitric oxide and regulation of vascular tone; pharmacological and physiological consideration. Am J Crit Care 7:131–140
4. Ballard SA, Gingell CJ, Tang K, Turner LA, Price ME, Naylor AM (1998) Effect of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isoenzymes. J Urol 159:2164–2171

## Clinical/Scientific Notes

Roberto Gazzeri, MD  
Massimiliano Neroni,  
MD  
Marcelo Galarza, MD  
Stefano Esposito, MD

### INTRACEREBRAL HEMORRHAGE ASSOCIATED WITH USE OF TADALAFIL (CIALIS)

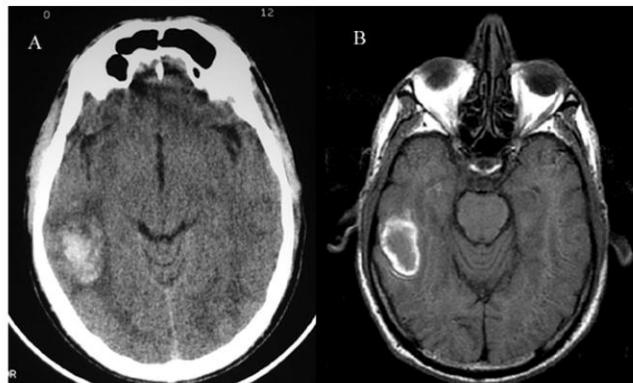
Tadalafil (Cialis; Eli Lilly, Indianapolis, IN), a phosphodiesterase type 5 (PDE5) inhibitor, is used to treat erectile dysfunction in men. The most common adverse effects reported include headache, dizziness, minor visual changes, and ischemic optic neuropathy.<sup>1</sup> We describe a patient who developed intracerebral hemorrhage after taking two tablets of tadalafil 20 mg.

**Case report.** A 70-year-old man presented to our emergency department with headache, nausea, and vomiting lasting for 4 days. He was anxious and confused, with memory disturbances, but neurologic examination was otherwise normal. His medical history included prostate cancer, erectile dysfunction, and depression. There was no history of hypertension, head trauma, or prior cerebrovascular disease (stroke/TIA), and no underlying vascular or hemostatic risk factors. Blood pressure and pulse measured were 132/65 mm Hg and 78 bpm. A head CT scan without contrast showed an intracerebral hemorrhage (2 × 4 cm in diameter) in the right temporal lobe (figure, A). During admission the patient volunteered that he had taken two tablets of tadalafil 20 mg (total 40

mg) to enhance his sexual performance 1 hour before onset of his acute headache and that his symptoms worsened moderately during his sexual intercourse. A head CT angiography showed no vascular anomalies or malformations. The patient was discharged after 7 days with no further headache and improvement of his neurologic symptoms. A brain MRI/angiography performed 1 month after admission revealed the hypointense lesion with a surrounding rim of hyperintensity on T1-weighted images, with no contrast enhancement and no evidence of underlying vascular malformation (figure, B).

**Discussion.** Tadalafil (Cialis), sildenafil (Viagra, Pfizer Ltd.), and vardenafil hydrochloride (Levitra, Bayer Pharmaceutical Corp.) are phosphodiesterase type 5 (PDE5) inhibitors approved for the treatment of erectile dysfunction: they enhance penile erection by relaxing smooth muscles and increasing blood flow in the corpus cavernosum. Various side effects associated with the use of these medications have been reported: headache, facial flushing, hypotension, and dizziness. Minor visual changes and ischemic optic neuropathy with subsequent loss of vision are also described as side effects of these drugs.<sup>1</sup> Rare hemorrhagic adverse

**Figure** Axial head CT scan and brain axial magnetic resonance T1-weighted image



(A) Axial head CT scan image shows an intracerebral hemorrhage in the right temporal lobe (2 × 4 cm in diameter). (B) Brain axial magnetic resonance T1-weighted image performed 1 month after admission shows a hypointense lesion with a surrounding rim of hyperintensity.

events include epistaxis and bleeding from esophageal varices and from hemorrhoids.<sup>2</sup> Cerebrovascular hemorrhage is extremely rare, but has been described after ingestion of sildenafil and verdenafil.<sup>3-5</sup> Although cerebral amyloid angiopathy is a potential cause of intracerebral hemorrhage in the elderly, in our patient's history there was no genetic risk factor and no evidence of old petechial bleeds on MRI; the onset of neurologic symptoms within a narrow time window after taking tadalafil suggests the hypothesis of a strict correlation between hemorrhage and drug abuse. In our case, we hypothesize that the abuse of this drug may have altered cerebral autoregulation with resultant abnormal cerebral arterial vasodilation followed by regional cerebral ischemia, infarction, and subsequent hemorrhage. Only three case reports of intracerebral hemorrhage after PDE5 inhibitor medications have been described; our case suggests that tadalafil should be used at the dose recommended by the manufacturer. In our case, the trigger for intracerebral hemorrhage appears to have been the ingestion of two tablets of tadalafil 20 mg, despite the manufacturer's advice (recommended

starting dose 10 mg). This potential adverse effect should be considered by physicians involved in the treatment of patients with erectile dysfunction.

From the Department of Neurosurgery, San Giovanni Ad-dolorata Hospital, Rome, Italy.

*Disclosure:* The authors report no conflicts of interest.  
Received May 18, 2007. Accepted in final form August 14, 2007.

*Address correspondence and reprint requests to Dr. Roberto Gazzera, Department of Neurosurgery, San Giovanni Ad-dolorata Hospital, Rome, Italy; robertogazzera@gmail.com*

Copyright © 2008 by AAN Enterprises, Inc.

1. Buxton N, Flannery T, Wild D, Bassi S. Sildenafil (Viagra)-induced spontaneous intracerebral haemorrhage. *Br J Neurosurg* 2001;15:347-349.
2. Ismail H, Harries PG. Recurrent epistaxis after treatment with tadalafil (Cialis). *Acta Otolaryngol* 2005; 125:334-335.
3. McGee HT, Egan RA, Clark WM. Visual field defect and intracerebral hemorrhage associated with use of vardenafil (Levitra). *Neurology* 2005;64:1095-1096.
4. Monastero R, Pipia C, Camarda LK, Camarda R. Intracerebral haemorrhage associated with sildenafil citrate. *J Neurol* 2001;248:141-142.
5. Pomeranz HD. Can erectile dysfunction drug use lead to ischaemic optic neuropathy? *Br J Ophthalmol* 2006; 90:127-128.

J. Betts, PhD  
M.J. Barron, PhD  
S.J. Needham,  
FRCPath  
A.M. Schaefer, MBBS  
R.W. Taylor, PhD  
D.M. Turnbull, MD

#### GASTROINTESTINAL TRACT INVOLVEMENT ASSOCIATED WITH THE 3243A>G MITOCHONDRIAL DNA MUTATION

Defects of the mitochondrial genome (mtDNA) are increasingly recognized as common causes of neurologic syndromes.<sup>1</sup> One of the most common pathogenic mtDNA mutations is the m.3243A>G in the *MTTL1* gene. In addition to numerous neurologic features this mutation can also give rise to gastrointestinal symptoms including bloating, dysphagia, recurrent vomiting and anorexia, chronic diarrhea, and gastrointestinal pseudo-obstruction.<sup>2-4</sup> To gain insight into the pathophysiology of gastrointestinal symptoms associated with the m.3243A>G mtDNA mutation, we investigated the degree of respiratory chain deficiency and the level of m.3243A>G mutation in individual areas from the gastrointestinal tract of two patients in whom gastrointestinal symptoms were both prominent and difficult to manage.

**Case report.** Patient 1 developed many features of the mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS) syndrome including strokelike episodes, encephalopathy, myopathy, and lactic acidosis. In addition, she had a long history of digestive problems

dating back to childhood. She had a small appetite even as a child and felt full even with small portions. During her teenage years constipation became more marked, as well as a feeling of bloating after even a small meal. In later life she developed severe constipation requiring regular enemas and laxatives. She died at age 32 years.

Patient 2, who died at age 59 years, was the maternal aunt of Patient 1. She had a relatively late onset of symptoms, first presenting at the age of 43 years with migraine. She subsequently developed marked cognitive decline, cardiac failure, and deafness, but no strokelike episodes or seizures. She had few gastrointestinal problems in the early years of her disease course but constipation became progressively more severe over the last 5 years of life. She was given an altered diet, regular laxatives, and enemas, but even with these measures she became grossly distended with massive fecal loading.

At autopsy, the entire gastrointestinal tract from both patients was carefully examined and sampled. On gross examination, marked intestinal dilation was observed in Patient 2, accompanied by thinning of the bowel wall. In both patients, light microscopic examination revealed

Supplemental data at  
[www.neurology.org](http://www.neurology.org)

# Neurology®

## INTRACEREBRAL HEMORRHAGE ASSOCIATED WITH USE OF TADALAFIL (CIALIS)

Roberto Gazzetti, Massimiliano Neroni, Marcelo Galarza, et al.  
*Neurology* 2008;70:1289-1290  
DOI 10.1212/01.wnl.0000308939.16685.b6

This information is current as of April 7, 2008

### Updated Information & Services

including high resolution figures, can be found at:  
<http://n.neurology.org/content/70/15/1289.full>

### References

This article cites 5 articles, 2 of which you can access for free at:  
<http://n.neurology.org/content/70/15/1289.full#ref-list-1>

### Citations

This article has been cited by 1 HighWire-hosted articles:  
<http://n.neurology.org/content/70/15/1289.full##otherarticles>

### Permissions & Licensing

Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at:  
[http://www.neurology.org/about/about\\_the\\_journal#permissions](http://www.neurology.org/about/about_the_journal#permissions)

### Reprints

Information about ordering reprints can be found online:  
<http://n.neurology.org/subscribers/advertise>

*Neurology*® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright . All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.



# APPENDIX -13

Case Report

## Subarachnoid Hemorrhage and Intracerebral Hematoma due to Sildenafil Ingestion in a Young Adult

Hyoung-Soo Byoun, M.D.,<sup>1</sup> Young-Joon Lee, M.D.,<sup>2</sup> Hyeong-Joong Yi, M.D.<sup>1</sup>

Departments of Neurosurgery,<sup>1</sup> Neuroradiology,<sup>2</sup> Hanyang University Medical Center, Seoul, Korea

Sildenafil citrate (Viagra®; Pfizer US Pharmaceutical Group, New York, NY, USA) is a potent vasodilating agent to treat male erectile dysfunction. Among its adverse effects, hemorrhagic stroke has not been widely reported yet. We present a case of a 33-year-old healthy man who ingested 50 mg sildenafil a half hour before onset of headache, nervousness and speech disturbance. Head computed tomogram of this stuporous man showed huge intracerebral hemorrhage and thick subarachnoid hemorrhage, but angiography failed to disclose any vascular anomalies. Subsequent surgical procedure was followed, and rehabilitation was provided thereafter. Sildenafil seems to act by redistributing arterial blood flow, and concurrent sympathetic hyperactivity, which lead to such hemorrhagic presentation. Extreme caution should be paid on even in a young adult male patient even without known risk factors.

**KEY WORDS :** Intracerebral hemorrhage · Risk factors · Sildenafil · Subarachnoid hemorrhage.

### INTRODUCTION

For a decade, sildenafil citrate (Viagra®; Pfizer US Pharmaceutical Group, New York, NY, USA) has become one of the top-selling product in the world-wide market for male impotence treatment. Since its first introduction however, numerous adverse effects have been reported, and particular attention should be paid upon when prescription is considered. With regard to intracerebral hemorrhage (ICH), there are only four English written literatures<sup>1,4,9,10</sup>. All of these cases showed minimal-to-moderate degree hemorrhage with unremarkable recovery.

We experienced a case of massive ICH associated with subarachnoid hemorrhage (SAH) requiring surgical removal. This young male patient did not have any risk factors for hemorrhage. A detailed case report and possible pathophysiological explanations are presented.

### CASE REPORT

A 33-year-old man was brought in to the Emergency Room for sudden unconsciousness following paroxysmal headache, nervousness and speech disturbance of two-hour duration. Approximately a half hour prior to symptom onset, he ingested one tablet of 50 mg sildenafil citrate to attempt sexual intercourse, but he could not.

Although he was slightly overweight (178 cm, 88 kg), he had been healthy and free of any significant medical history, including arterial hypertension, diabetes, hyperlipidemia, migraine, pre-existing cardiovascular or cerebrovascular diseases. He took no other medications, except episodic common-cold remedies. He had a 15-year history of tobacco smoking (approximately 1 pack per day), and ingested irregular alcohol about two times per week, presumably more than social drinking. He had been married 35 days before this event, and had taken sildenafil citrate 25 mg for two times during recent 2 weeks that were prescribed by a urologist. His wife denied any similar symptoms when used previously.

On admission, he was profoundly stuporous, densely quadriparetic (Grade 3/Grade 1), and had fully dilated pupils. Vital signs showed high blood pressure of 160/95 mmHg,

• Received : March 16, 2009 • Revised : July 20, 2009  
• Accepted : January 6, 2010  
• Address for reprints : Hyeong-Joong Yi, M.D.  
Department of Neurosurgery, Hanyang University Medical Center,  
Haengdang-dong, Seongdong-gu, Seoul 133-792, Korea  
Tel : +82-2-2290-8499, Fax : +82-2-2281-0954  
E-mail : hjiy18499@hanyang.ac.kr

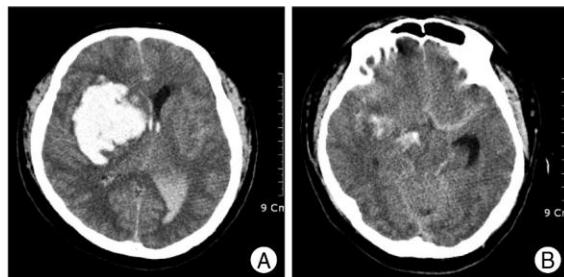
rapid pulse rate (108/min) and respiration (24/min), and fever up to 38.5°C, respectively. Brain computed tomography (CT) showed a huge ICH on the right basal ganglia, intraventricular clots and thick SAH (Fig. 1). A CT angiography and transfemoral catheter angiography (TFCA) failed to disclose any vascular lesion on the corresponding hemisphere (Fig. 2).

Because of impending herniation, we hurried him into the operating room for decompression. Following dural reflection, swollen brain was encountered, and prompt temporal corticectomy was conducted to find organizing hematoma. After gentle suction and irrigation of hematoma, the sylvian fissure was widely split to show most course of the right middle cerebral artery (MCA). From distal portion, the MCA was thoroughly inspected up to the proximal MCA, but we could not find any aneurysmal dilatation or other angiomatic lesions. Meticulous hemostasis and expansive duroplasty was done. Skull flap was not covered to control raised intracranial pressure.

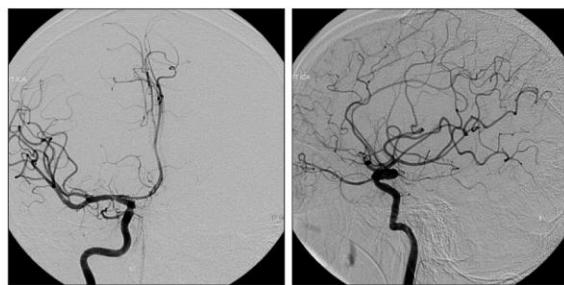
Postoperatively, he remained stuporous, but motor function was slightly improved (Grade 5/Grade 1). While in the intensive care unit stay, blood laboratory tests and serologic tests were undertaken, but there were no proven clues for the intracranial bleeding. Afterwards, robust rehabilitation was followed, and cerebrospinal fluid diversion and cranioplasty was performed for delayed hydrocephalus and skull defect, at postoperative 40 days (Fig. 3). At the last follow-up visit, 18 months postoperatively, he regained consciousness, was able to communicate with care givers in restricted extent, but was still hemiparetic (Grade 5/Grade 3) on wheel-chair and dependent for commanding major activities of daily living.

## DISCUSSION

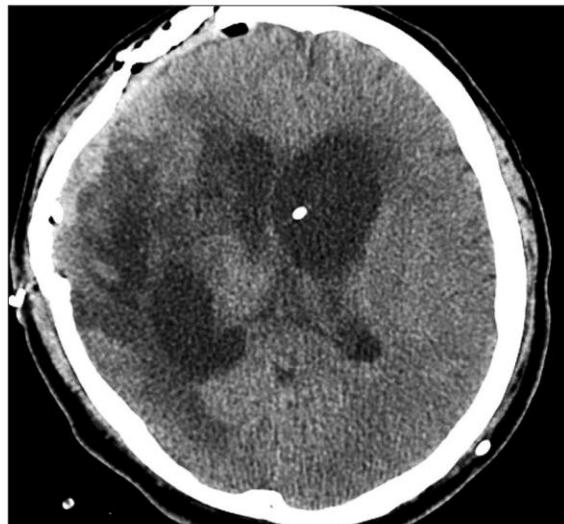
Causes of ICH in a non-hypertensive subject are largely divided into structural vascular anomalies (arteriovenous malformation, aneurysm, moyamoya disease, amyloid angiopathy), and dysfunctional coagulation (coagulopathy, drugs). Drug-induced ICH is mostly attributed to anticoagulants, thrombolytics, sympathomimetics, metamphetamines, or cocaine<sup>1</sup>. Although there are four previous reports about ICH after sildenafil use, all of these were manifested as minimal volume hemorrhage in elderly with risk factors and thus, surgical evacuation was not required<sup>1,4,9,10</sup>. The present case mimics either diffuse, thick SAH from rupture of the proximal MCA aneurysm, or massive ICH leaking into the ventricles and subarachnoid space. With the aid of angiography, possibility of vascular anomaly was discarded. The cause and effect relationship of sildenafil and ICH herein,



**Fig. 1.** Admission head computed tomograms show huge hemorrhage on the right basal ganglia and ventricles (A), in addition to diffuse subarachnoid hemorrhage (B).



**Fig. 2.** Right carotid angiograms only show displacement of the anterior and middle cerebral arteries without any anomalous cerebral vasculatures.



**Fig. 3.** A computed tomograms scan following cranioplasty and ventriculoperitoneal shunting obtained on postoperative 3rd day.

can be established when considering close temporal relationship between sildenafil ingestion and onset of neurological symptoms, within 2 to 4 hours of presumed peak level in blood, due to ICH in a patient without risk factors and non-specific blood laboratory results<sup>6,14</sup>.

Sildenafil (UK-92,480), an orally active, selective inhibitor of phosphodiesterase type 5 (PDE-5), is a crucial regulator of cyclic guanosine monophosphate (cGMP) and at first

intention, it is manufactured aiming at the corpus cavernosum of the human male. It plays a role in causing muscle relaxation, vasodilatation and penile erection by increasing concentration of cGMP and nitrous oxide (NO) in the smooth muscle of the corpus cavernosum<sup>3)</sup>. Side effects of sildenafil, including flushing, headache, nasal congestion, and changes in pulmonary blood flow can tell us that such vasodilatory effect is not confined to the corpus cavernosum<sup>11,12)</sup>. This drug also redistributes the arterial flow, and decreases perfusion, consequently may lead to acute myocardial infarction. For the above reasons, it lowers systolic blood pressure by 8 to 10 mmHg in clinical trials<sup>14)</sup>.

Several ischemic manifestations, such as transient ischemic attack, ischemic stroke, cerebral infarction, or ischemic optic neuropathy can be explained by the above mechanisms<sup>8)</sup>. Vasodilatory effect of sildenafil may also cause atrial fibrillation, provoke atrial thrombi and cardioembolism in a pre-existing cardiomyopathic patient by increasing pressure gradient over the left ventricular outflow tract<sup>2)</sup>. On the other hand, hypotension could lead to secondary sympathetic hyperactivity<sup>8,12)</sup>. Hypotension, cardiac arrhythmia, and rebound sympathetic hyperactivity seems to play concerted roles in producing stroke, especially in ischemic stroke. In previous literatures, we could not find any linear relationship between drug dosage (25 mg, 50 mg, 100 mg) and occurrence of stroke<sup>1,4,5,7-10)</sup>. But, all cases were associated with utilizing more than 50 mg once or twice in a short period. An unknown process of sensitization may be involved however, the mode of drug action in large part, may be not cumulative but idiosyncratic.

The reported occurrence of headache, dizziness, visual disturbances, retinal dysfunction, and a pupil-sparing oculomotor palsy suggest that sildenafil affects regulation of the cerebral microvasculature. In addition to a selective action on PDE-5, sildenafil may act on other two types of PDE (PDE-1 and PDE-2), which are involved in control of cerebral vasculature<sup>6,13)</sup>. To date, there has been no clear evidence to explain pertinent mechanisms of ICH associated with sildenafil.

In summary, sildenafil may act by redistributing arterial blood flow, hence rendering brain tissue more inappropriate perfusion, presenting as prodromes of headache, nervousness and speech disturbance as shown in the current case. Ensuing sympathetic hyperactivity through PDE-1 and PDE-2 might lead to rupture of vessels. Although it is contrary to common belief, we suggest that these inciting and propagating factors for ICH even in a young adult

male patient without known risk factors should be warned before prescribing sildenafil.

## CONCLUSION

Sildenafil is a potentially dangerous drug, which can provoke life-threatening ICH and SAH in a young adult male. When considering usage, careful discussion and pre-medication work-up with urologist is mandatory. Adverse effect, such as headache, nervousness, dizziness or speech disturbance should be promptly diagnosed to minimize sequelae.

## References

- Alpsan MH, Bebek N, Ciftci FD, Coban O, Bahar S, Tuncay R : Intracerebral hemorrhage associated with sildenafil use : a case report. *J Neurol* 255 : 932-933, 2008
- Awani GM, Calderon E, Dawood G, Alpert MA : Acute, symptomatic atrial fibrillation after sildenafil citrate therapy in a patient with hypertrophic obstructive cardiomyopathy. *Am J Med Sci* 320 : 69-71, 2000
- Ballard SA, Gingell CJ, Tang K, Turner LA, Price ME, Naylor AM : Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes. *J Urol* 159 : 2164-2171, 1998
- Buxton N, Flannery T, Wild D, Bassi S : Sildenafil (Viagra)-induced spontaneous intracerebral haemorrhage. *Br J Neurosurg* 15 : 347-349, 2001
- Egan RA, Pomeranz H : Transient ischemic attack and stroke associated with sildenafil (Viagra) use. *Neurology* 59 : 293-294, 2002
- Farooq MU, Naraveta B, Moore PW, Majid A, Gupta R, Kassab MY : Role of sildenafil in neurological disorders. *Clin Neuropharmacol* 31 : 353-362, 2008
- Habek M, Petracić D : Stroke--an adverse reaction to sildenafil. *Clin Neuropharmacol* 29 : 165-167, 2006
- Kim KK, Kim DG, Ku YH, Lee YJ, Kim WC, Kim OJ, et al. : Bilateral cerebral hemispheric infarction associated with sildenafil citrate (Viagra) use. *Eur J Neurol* 15 : 306-308, 2008
- Martí I, Martí Massó JF : Hemiballism due to sildenafil use. *Neurology* 63 : 534, 2004
- Monastero R, Pipia C, Camarda LK, Camarda R : Intracerebral haemorrhage associated with sildenafil citrate. *J Neurol* 248 : 141-142, 2001
- Morales A, Gingell C, Collins M, Wicker PA, Osterloh IH : Clinical safety of oral sildenafil citrate (VIAGRA) in the treatment of erectile dysfunction. *Int J Impot Res* 10 : 69-73; discussion 73-74, 1998
- Morgan JC, Alhatou M, Oberlies J, Johnston KC : Transient ischemic attack and stroke associated with sildenafil (Viagra) use. *Neurology* 57 : 1730-1731, 2001
- Uthayathas S, Karuppagounder SS, Thrash BM, Parameshwaran K, Suppiraniam V, Dhanasekaran M : Versatile effects of sildenafil : recent pharmacological applications. *Pharmacol Rep* 59 : 150-163, 2007
- Zusman RM, Morales A, Glasser DB, Osterloh IH : Overall cardiovascular profile of sildenafil citrate. *Am J Cardiol* 83 : 35C-44C, 1999

- tional objectives for postgraduate year one (PGY1) pharmacy residency programs, 2nd edition. [www.ashp.org/DocLibrary/Accreditation/PGY1-Goals-Objectives.aspx](http://www.ashp.org/DocLibrary/Accreditation/PGY1-Goals-Objectives.aspx) (accessed 2011 Apr 11).
2. American Society of Health-System Pharmacists. Residency update 2009. [www.ashp.org/DocLibrary/Accreditation/ASD\\_ResidencyTownhallUpdateMCM2008.pdf](http://www.ashp.org/DocLibrary/Accreditation/ASD_ResidencyTownhallUpdateMCM2008.pdf) (accessed 2010 Jun 11).
  3. Rosenberg JM, Schilit S, Nathan JP et al. Update on the status of 89 drug information centers in the United States. *Am J Health-Syst Pharm.* 2009; 66:1718-22.

**Heather J. Ipema, Pharm.D.**, Clinical Assistant Professor  
heatheripema@gmail.com

**Amy E. Lodolce, Pharm.D., BCPS,**  
Assistant Director

**Carissa E. Mancuso, Pharm.D.**, Clinical Assistant Professor

Drug Information Group  
College of Pharmacy  
University of Illinois at Chicago

833 South Wood Street, Room 164  
Chicago, IL 60612

*The research assistance of Frank Paloucek, Pharm.D., DABAT, is acknowledged.*

*The authors have declared no potential conflicts of interest.*

DOI 10.2146/ajhp100360

## Subarachnoid hemorrhage associated with tadalafil

Tadalafil is a phosphodiesterase type-5 (PDE5) inhibitor indicated for the treatment of erectile dysfunction. Inhibition of the PDE5 isoenzyme, which is responsible for degradation of cyclic guanosine monophosphate in the corpus cavernosum, will ultimately enhance the effect of nitric oxide and, consequently, the relaxation of the vascular smooth muscle in the corpus cavernosum and penile erection after sexual stimulation. Tadalafil is the longest-acting PDE5 inhibitor, with an elimination half-life of 17.5 hours and up to 36 hours' duration of effect. The drug has been associated with headache, flushing, dizziness, visual disturbances, and hypotension.<sup>1</sup>

A 45-year-old previously healthy man arrived at the emergency department with a severe headache of five hours' duration associated with one episode of vomiting. There was no decrease in the level of consciousness, no focal neurologic deficit, and no convulsive activity. The patient was previously healthy, with no history of diabetes mellitus, hypertension, cerebrovascular disease, trauma, or bleeding disorders and denied taking any prescription medication, over-the-counter medicine, or herbal products. The patient's family and social histories were unremarkable. On examination, he was agitated and in severe discomfort due to the headache. He reported tak-

ing one 20-mg tablet of tadalafil a few hours before the onset of symptoms and stated that he had started taking tadalafil recently "as needed" without consulting a health care provider. A computed tomography (CT) scan of his head revealed a subarachnoid hemorrhage (SAH) (3 × 4 cm in diameter); CT angiography of the head showed no vascular abnormalities or aneurysmal malformations. An electrocardiogram and a chest radiograph were normal, and all laboratory test values and vital signs were within normal limits. The patient had an uneventful four-day stay in the intensive care unit; he received 60 mg of nimodipine orally very four hours and was discharged home.

This patient's adverse reaction can be attributed to tadalafil because of the temporal relationship between use of the drug and the SAH. The probable association of the event with tadalafil use is enhanced by the fact that the patient had no risk factors for developing an SAH, and no underlying etiology was evident. Use of the Naranjo et al.<sup>2</sup> adverse-reaction probability scale revealed a probable association between the SAH and tadalafil (score of 6). In addition, a PubMed search about this probable association revealed two cases of intracerebral hemorrhage (ICH) associated with the use of tadalafil. Steeves et al.<sup>3</sup> reported a possible associa-

tion between tadalafil use and arteriovenous malformation (AVM) hemorrhage during coitus in a 59-year-old man. The AVM was excised, and the patient made an uneventful recovery. Gazzeri et al.<sup>4</sup> described an ICH in a 70-year-old man without evidence of any vascular anomalies who took 40 mg of tadalafil to enhance his sexual performance one hour before the onset of symptoms. The patient was discharged from the hospital after seven days with improvement in neurologic symptoms. Six cases of SAH or ICH have been reported after the ingestion of sildenafil,<sup>5-10</sup> and a single case of ICH was reported in a patient taking vardenafil.<sup>11</sup>

Tadalafil can inhibit PDE5, which is found in platelets. This can lead to the inhibition of platelet activation and aggregation.<sup>12</sup> On the other hand, nitric oxide induces relaxation of vascular smooth muscles. Platelet inhibition combined with increased cerebral blood flow may be associated with an increased risk of SAH.<sup>9</sup> Although tadalafil has not been shown to increase bleeding times in healthy patients, the manufacturer recommends that caution be exercised in patients with bleeding disorders or significant active peptic ulceration.<sup>1</sup>

Given the potential risk of hemorrhagic stroke after the ingestion of tadalafil, clinicians should be cautious when prescribing this medication and should consider this agent as a potential cause of cerebral hemorrhage in patients with no other underlying etiology or risk factors.

1. Cialis (tadalafil) product package insert. Indianapolis: Eli Lilly and Company; 2010.
2. Naranjo CA, Bust U, Sellers EM et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981; 30:239-45.
3. Steeves TD, Jones LK, Ecker RD et al. Coital hemorrhage of an arteriovenous malformation after premedication with tadalafil (Cialis). *J Stroke Cerebrovasc Dis*. 2005; 14:179-81.
4. Gazzera R, Neroni M, Galarza M et al. Intracerebral hemorrhage associated with use of tadalafil (Cialis). *Neurology*. 2008; 70:1289-90.
5. Kaneria MV, Pagar S, Samant H et al. Subarachnoid haemorrhage: possibly caused by the illegitimate use of sildenafil citrate. *J Assoc Physicians India*. 2008; 56:809-11.
6. Alpsan MH, Bebek N, Ciftci FD et al. Intracerebral hemorrhage associated with sildenafil use: a case report. *J Neurol*. 2008; 255:932-3.
7. Mehdizadeh M, Hosseini H, Yazdchi T et al. Visual field defect as a presenting sign for hemorrhagic stroke caused by sildenafil. *Indian J Ophthalmol*. 2008; 56:159-60.
8. Monastero R, Pipia C, Camarda LK et al. Intracerebral haemorrhage associated with sildenafil citrate. *J Neurol*. 2001; 248:141-2.
9. Buxton N, Flannery T, Wild D et al. Sildenafil (Viagra)-induced spontaneous intracerebral haemorrhage. *Br J Neurosurg*. 2001; 15:347-9.
10. Kaneria MV, Pagar S, Samant H et al. Subarachnoid haemorrhage: possibly caused by the illegitimate use of sildenafil citrate. *J Assoc Physicians India*. 2008; 56:809-11.
11. McGee HT, Egan RA, Clark WM. Visual field defect and intracerebral hemorrhage associated with use of vardenafil (Levitra). *Neurology*. 2005; 64:1095-6.
12. McHugh J, Cheek DJ. Nitric oxide and regulation of vascular tone: pharmacological and physiological considerations. *Am J Crit Care*. 1998; 7:131-40.

**Marwan Sheikh-Taha, Pharm.D., BCPS (AQ Cardiology), Clinical Associate Professor**  
marwan.taha@lau.edu.lb

**Rayan Abu Alaywa, Pharm D., Community Pharmacist**

School of Pharmacy  
Lebanese American University  
P.O. Box 36  
Byblos, Lebanon

*The authors have declared no potential conflicts of interest.*

DOI 10.2146/ajhp100506

## A Web-based experiential rotation platform

Today's college students may require different approaches to teaching and learning. The so-called "video-game generation" currently populating the majority of pharmacy schools is adept at using technology and seems to respond well to interactive teaching techniques.<sup>1</sup> Efforts to increase the use of technology to engage students in learning have been met with some success.<sup>2-4</sup> To date, little has been reported outside the classroom setting regarding the use of technology to individualize a student's experience or the integration of technology into the clinical experiences of a pharmacy residency program.<sup>5</sup>

Currently, several colleges of pharmacy use Web platforms to serve as a hub for students and preceptors at rotation sites.<sup>6</sup> Our institution effectively uses this type of system to distribute important announcements, view student and preceptor schedules, and complete evaluations. Recently, we began exploring the use of a Web-based platform (Microsoft SharePoint, Microsoft Corp., Redmond, WA) to organize and shepherd students through common advanced pharmacy practice experiences (APPEs) at our institution, as well as coordinate the rotation experiences of pharmacy residents. For preceptors, this technology affords numerous advantages, which are described below.

Microsoft SharePoint is an integrated server program within the Microsoft Office system.<sup>7</sup> This platform enables preceptors to customize a website specific to their rotation. Students are provided with immediate and ongoing access to the overall rotation description, expectations, and assignments.

One of the benefits of using this type of technology for experiential education is its customizability. Preceptors are free to upload documents, design student-controlled pages (e.g., blogs), and develop calendars. Users are granted permission to view, modify, and control content by the preceptor. We have chosen an approach that will allow each rotation site to have a similar structure

while maintaining preceptors' autonomy regarding content. This should provide some familiarity for students who have several APPEs. In addition, a core group of preceptors can facilitate a site template and design for those preceptors less comfortable with the process. Residents also frequently engage in these rotation experiences and can have materials and resources specific to their level of expertise and rotation objectives layered into each rotation site.

At its most basic level, the rotation website can be used to house the basic information a student or resident may need for the rotation experience. Links to the current syllabus, contact information, and a rotation calendar are common components of our rotation websites. Learning modules can add another layer of content to the website. Another approach to developing content for these Web pages may be to have each student or resident create a concise summary on a topic. This succinct, one- or two-page primer on a specific topic could serve as the initial content for each module. In combination with a library of representative readings and online resources, each module page can be a complete mixed media resource that students and residents can access at any point during the rotation experience.

SharePoint also enables the construction of "wiki" and blog pages. This function would permit students to keep a journal of their experiences for the month (e.g., unique patient cases encountered, drug information pearls learned, key concepts or queries that required time and effort to research). In addition, because the entire website is searchable, each topic recorded on the journal page is then part of the content on the site and viewable from the primary content pages.

As with any new educational tool, the effectiveness of this Web-based module will need to be assessed. We believe that two global areas should be addressed in the assessment of this type of edu-

*Continued on page 1198*



Received: 05.12.2013 / Accepted: 02.02.2014

DOI: 10.5137/1019-5149.JTN.9995-13.1



Case Report

# Subarachnoid and Intracerebral Hemorrhage After Alcohol Ingestion and Illicit Use of Sildenafil

## *Reçetesiz Sildenafil ile Alkol Kullanımı Sonrası Gelişen Subaraknoid Kanama ve Intraserebral Hematom*

Veysel ANTAR, Neslihan Hatice KOKSAL SUTPIDELER, Oğuz BARAN, Gorkem BITIRAK

*Istanbul Research and Education Hospital, Department of Neurosurgery, Istanbul, Turkey*

Corresponding Author: Veysel ANTAR / E-mail: veyselantar@hotmail.com

### ABSTRACT

Sildenafil is a drug used in the treatment of male impotence. Few cases of spontaneous intracerebral hemorrhage following the use of sildenafil have been cited in the literature. A 42-year-old man was admitted to the emergency outpatient clinic of Istanbul Educational and Research Hospital after sudden loss of consciousness. He had ingested alcohol, taken 50mg sildenafil and had sexual intercourse. Non-contrast cranial tomography revealed an intracerebral hematoma with extension to the ventricles.

Sildenafil is a selective phosphodiesterase-5 enzyme inhibitor. With the inhibition of PDE-5, the amount of cyclic-guanosine monophosphate (c-GMP) in the smooth vascular muscle cells in the corpus cavernosum increases, leading to a relaxation of muscles and vasodilatation. Studies have shown that the NO-c-GMP pathway leads to cerebral vasodilatation with a similar mechanism. The literature has shown that the effect of PDE-1 and PDE-2 on cerebral bleeding control is affected by sildenafil. This increased blood flow increases the risk of intracranial haemorrhage. Although data concerning the presentation of intracerebral hematoma in connection with the combined use of alcohol ingestion and use of sildenafil is inadequate, it can nevertheless be thought that the combined use increases the risk of spontaneous intracerebral hemorrhage and caution is in order concerning the matter.

**KEYWORDS:** Sildenafil, Intracerebral, Hemorrhage, Alcohol, Subarachnoid bleeding

### ÖZ

Sildenafil erkek impotansının tedavisinde kullanılan bir ilaçtır. Sayısı az olsa da literatürde sildenafil kullanımı sonrasında spontan intraserebral hemorajî olguları bildirilmiştir. Kırk iki yaşında bir erkek hasta anı bilinç kaybı sonrasında İstanbul Eğitim ve Araştırma Hastanesinin acil polikliniğine başvurdu. Alkol alıp, 50mg sildenafil kullanmış ve cinsel ilişkide bulunmuştur. Kontrastsız kraniyal tomografi ventriküllerde uzanan bir intraserebral hematom gösterdi.

Sildenafil selektif bir fosfodiesteraz-5 enzim inhibitörüdür. PDE-5 inhibitörleri ile korpus kavernosumda düz vasküler kas hücrelerinde siklik guanozin monofosfat (c-GMP) miktarı artıp kaslarda gevşeme ve vazodilatasyona yol açar. Çalışmalar NO-c-GMP yolağının benzer bir mekanizmaya serebral vazodilatasyona yol açtığını göstermiştir. Literatür, PDE-1 ve PDE-2'nin serebral kanama kontrolü üzerindeki etkisinin sildenafille etkilendiğini göstermiştir. Bu artmış kan akışı, intrakraniyal kanama riskini artırır.

Kombine alkol alma ve sildenafil kullanmayı bağıntılı olarak intraserebral hematom ortaya çıkmasına ilgili veriler yetersiz olsa da kombine kullanımın spontan intraserebral kanama riskini artırdığı ve bu konuda dikkatli olmak gerektiğini düşünülebilir.

**ANAHTAR SÖZCÜKLER:** Sildenafil, Intraserebral, Kanama, Alkol, Subaraknoid kanama

### INTRODUCTION

Sildenafil is a drug used in the treatment of male impotence. It has a direct effect on the vessels of the corpus cavernosum. Sildenafil acts on the corpus cavernosum by way of a raised concentration of c-GMP and NO in the smooth muscle cells. The increased c-GMP concentration leads to vasodilatation and the erection of the penis (7). In addition to this vascular reaction, other well-known side effects are flushing, headache and dizziness due to dilatation of the cerebral veins (10). Among its adverse effects, hemorrhagic stroke has not been widely reported yet (7). Although few cases of spontaneous intracranial hemorrhage following the use of sildenafil have been reported in the literature. We report a case of fatal

subarachnoid and intracerebral haemorrhage as a result of ingestion of alcohol and non-prescription use of sildenafil.

### CASE REPORT

A 42-year-old man was admitted to the emergency outpatient clinic of İstanbul Educational and Research Hospital after sudden loss of consciousness. He was said to have ingested alcohol, taken 50 mg sildenafil and had sexual intercourse. On admission, blood pressure was 210/130 mm Hg and pulse 88 per minute. The Glasgow Coma Scale score was 5 (no eye opening, no verbal response and flexion to pain). Non-contrast cranial tomography revealed an anterior interhemispheric bleeding with extension to all four ventricles (Figure1, 2). An



**Figure 1:** Non-contrast cranial tomography revealed an anterior interhemispheric bleeding with extension to all four ventricles (lateral ventricles).



**Figure 2:** Non-contrast cranial tomography revealed an anterior interhemispheric bleeding with extension to all four ventricles (fourth ventricle).

angiography would have preferably been performed but the patient's condition did not allow this. No other tests related to an increased risk of stroke could be performed. An external ventricular drain was placed and the patient was taken to the intensive care unit but he failed to respond to maximal therapy and died.

#### DISCUSSION

The reasons of non-traumatic intracerebral hemorrhage can be categorised as hypertension, non-hypertensive gross structural vascular anomalies (AVM, aneurysm, MoyaMoya disease, amyloid angiopathy, etc.), intracranial neoplasms, cerebral venous thrombosis, infection and dysfunctional coagulopathy. Drug-induced intracerebral haemorrhages are related to anticoagulant thrombolytics, sympathomimetics, methamphetamines or cocaine (1, 7). Cases of intracerebral hemorrhages in relation to sildenafil use are being increasingly reported recently (1, 3, 4, 7, 11).

Sildenafil is a selective phosphodiesterase-5 (PDE-5) enzyme inhibitor. With the inhibition of PDE-5, the amount of cyclic-guanosine monophosphatase (cGMP) in the vascular smooth muscle cells in the corpus cavernosum increases, leading to a relaxation of muscles and vasodilatation (1). Studies have shown that the NO-c-GMP pathway leads to cerebral vasodilatation with a similar mechanism (1, 4). Alspas et al. has shown that the effect of PDE-1 and PDE-2 on cerebral bleeding is affected by sildenafil. This increase in blood flow may increase the risk of intracranial haemorrhage (1).

The side effects of sildenafil are well known. There are side effects related to vascular structures such as headache, flushing, dizziness and nasal congestion (10).

Another result of the non-prescription use of the drug is usage in improper dose. The recommended starting dose of sildenafil should be 50 mg and the maximum dose within 24 hours should be 100 mg (10, 11).

Sildenafil is the best selling drug in the global market for the treatment of male impotence (7). In addition to the use of prescription sildenafil, the non-prescription use of the drug is significantly high due to the ease in access to the drug without a prescription.

In this study; an intracerebral hemorrhage case due to the ingestion of alcohol with sildenafil where surgical treatment was not possible is presented. Although there are cases of subarachnoid haemorrhage and intracerebral hemorrhage caused by the use of sildenafil, there are few cases in the literature reporting intracerebral or subarachnoid hemorrhage associated with the use of sildenafil (1, 7, 8, 11, 10).

Sildenafil is not reported to interact with ASA, antiacids and alcohol (6). It is difficult to understand the effects of alcohol ingestion in cases of intracranial hemorrhage caused by the combined ingestion of sildenafil with alcohol. There are reports in literature that point to a possible relationship between the ingestion of alcohol and spontaneous intracerebral

hemorrhage (2, 6, 9). There is no data suggesting an increase in the risk of spontaneous intracerebral hemorrhage due to combined ingestion of alcohol and sildenafil. However, our spontaneous intracerebral hemorrhage case after ingestion of alcohol and sildenafil indicates that this could be a harmful combination.

#### CONCLUSION

Although there is inadequate data to connect intracerebral hemorrhage to the combined use of alcohol ingestion and non-prescription use of sildenafil, caution should be exercised about drinking alcoholic beverages when using sildenafil as this may increase the risk of spontaneous intracerebral hemorrhage.

#### REFERENCES

1. Alpsan MH, Bebek N, Ciftci FD, Coban O, Bahar S, Tuncay R: Intracerebral hemorrhage associated with sildenafil use: Case report. *J Neurol* 255:932-933,2008
2. Ariesen MJ, Claus SP, Rinkel GJ, Algra A: Risk factors for intracerebral hemorrhage in the general population: A systematic review. *Stroke* 34(8):2060-2065,2003
3. Boyoun HS, Lee YJ, Yi HJ: Subarachnoid hemorrhage and intracerebral hematoma due to sildenafil ingestion in a young adult. *J Korean Neurosurg Soc* 47:210-212,2010
4. Buxton N, Flannery T, Wild D, Bassi S: Sildenafil (Viagra)-induced spontaneous intracerebral haemorrhage. *Br J Neurosurg* 15(4):347-349,2001
5. Casolla B, Dequatre-Ponchelle N, Rossi C, Hénon H, Leys D, Cordonnier C: Heavy alcohol intake and intracerebral hemorrhage: Characteristics and effect on outcome. *Neurology* 79(11):1109-1115,2012
6. Eardley I: The role of phosphodiesterase inhibitors in impotence. *Exp Opin Invest Drugs* 6:1803-1810,1997
7. Kaneria MV, Pagar S, Samant H, Yeole S, Patil S: Subarachnoid haemorrhage: Possibly caused by the illegitimate use of sildenafil citrate. *J Assoc Physicians India* 56:809-811,2008
8. Leppala JM, Virtamo J, Fogelholm R, et al: Different risk factors for different stroke subtypes: Association of blood pressure, cholesterol, and antioxidants. *Stroke* 30(12):2535-2540,1999
9. McHugh J, Cheek DJ: Nitric oxide and regulation of vascular tone: pharmacological and physiological consideration. *Am J Crit (7):131-140,1998*
10. O'Donnell MJ, Xavier D, Liu L, et al: Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): A case-control study. *Lancet* 376(9735):112-123,2010
11. Samada K, Shiraishi H, Aoyagi J, Momoi MY: Cerebral hemorrhage associated with sildenafil. *Pediatr Cardiol* 30:998-999,2009
12. Zhang Y, Tuomilehto J, Jousilahti P, et al: Lifestyle factors on the risks of ischemic and hemorrhagic stroke. *Arch Intern Med* 171(20):1811-1818, 2011

# Intracranial aneurysm and sildenafil

Avinash Adiga, MD, Hawa Edriss, MD, and Kenneth Nugent, MD

Sildenafil is one of the most commonly used drugs for the treatment of erectile dysfunction. To date, we found five reported cases of intracerebral bleeding and two reported cases of subarachnoid hemorrhage related to sildenafil use. We report a 49-year-old hypertensive and diabetic patient who presented with acute pulmonary edema and loss of consciousness following ingestion of 100 mg of sildenafil prior to sexual intercourse. He was not previously aware of the presence of an aneurysm and had no family history of it. Computed tomography of his head revealed a subarachnoid hemorrhage due to rupture of a saccular aneurysm with subsequent repeat hemorrhage within a few hours of presentation. A sudden increase in blood pressure led to pulmonary edema. Studies have shown that sildenafil acts on phosphodiesterase-1, -2 and -5 receptors and leads to a secondary increase in intracerebral circulation and vaso-dilatory effects, leading to sympathetic overactivity which increases the risk for intracranial bleeding.

**S**ildenafil, marketed as Viagra, is a widely used phosphodiesterase (PDE)-5 inhibitor to treat male sexual/erectile dysfunction and to increase libido and sexual performance. The common adverse effects of this drug include headache, flushing, indigestion, and impaired vision. Five cases of intracerebral bleeding and two cases of subarachnoid hemorrhage (SAH) due to sildenafil use have been reported (1–7). We report a 49-year-old man who presented with a hypertensive crisis and an SAH caused by rupture of a saccular intracranial aneurysm during sexual intercourse following sildenafil intake.

## CASE REPORT

A 49-year-old man with diabetes mellitus and hypertension was brought in to the emergency department due to acute-onset shortness of breath and loss of consciousness during sexual intercourse. The patient had ingested 100 mg of sildenafil prior to the event (unknown time gap). Reportedly, he was diaphoretic and short of breath and required intubation due to a low Glasgow Coma Scale score of <7. His blood pressure was 181/105 mm Hg with a mean arterial pressure of 124 mm Hg. His chest examination revealed bibasilar crackles. A neurological examination was not completed because the patient was sedated. His pupils were round and reactive with normal deep tendon reflexes, and he could localize the pain. Routine blood counts, platelet

counts, and coagulation factors were normal. His chest x-ray revealed diffuse bilateral opacities consistent with pulmonary edema. An electrocardiogram showed a normal sinus rhythm. An arterial blood gas showed high anion gap (29) metabolic acidosis with respiratory acidosis: pH 7.22; partial pressure of oxygen, 68 mm Hg; partial pressure of carbon dioxide, 42.7 mm Hg; bicarbonate, 17.1 mEq/L; and lactate, 4.7 mmol/L. Bedside transthoracic echocardiography showed normal systolic function with no regional wall motion abnormality and grade II diastolic dysfunction.

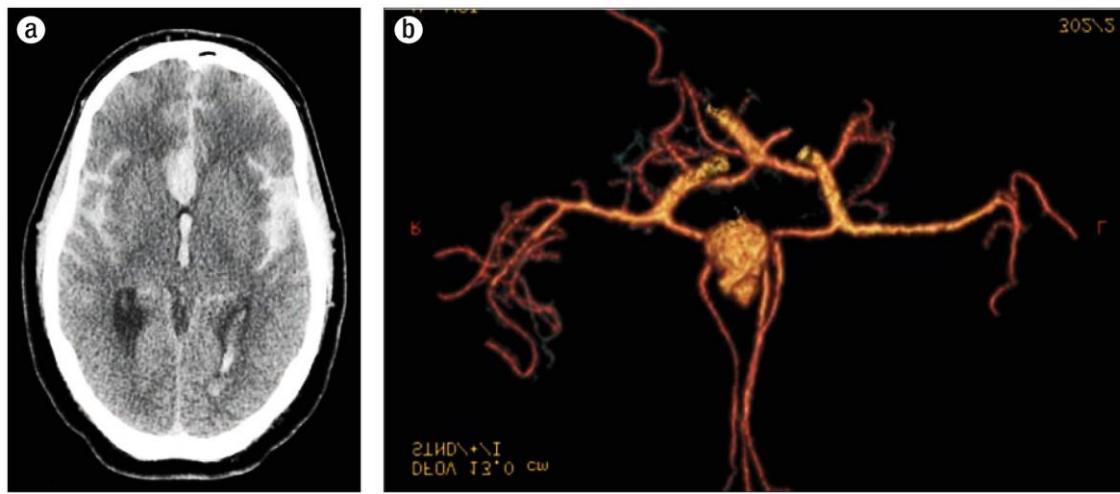
Computed tomography of the head showed a massive acute SAH with the largest blood collection in the area of the anterior communicating artery with mild hydrocephalus (*Figure 1a*). The patient was started on mannitol 100 g over 30 minutes and underwent computed tomography angiogram of intracranial vessels, which showed an aneurysm at the junction of the right anterior cerebral artery and anterior communicating artery (*Figure 1b*). He was urgently taken to the operating room and underwent ventriculostomy. While in the operating room, his ventricular pressures increased, his pupils dilated, suggesting brain herniation, and he underwent bilateral decompressive craniotomy and aneurysm clipping. Postoperatively, his Glasgow Coma Scale score was 3/15, and he was cooled to maintain temperature around 35°C for 48 hours. Because of his low Glasgow Coma Scale score, his chances for safe extubation seemed unlikely, and a tracheostomy and percutaneous endoscopic gastrostomy tube were placed on postoperative day 8. On postoperative day 10, he started to improve slowly, and his Glasgow Coma Scale increased to 15/15 on postoperative day 31. He continued to require a tracheostomy collar and was discharged to a neurorehabilitation institute.

## DISCUSSION

Sildenafil inhibits PDE-5-mediated hydrolysis of cyclic guanosine monophosphate (cGMP), leading to increased intracellular cGMP levels in the vascular smooth muscle of the corpus cavernosum and resulting in smooth muscle relaxation and arterial vasodilation (8). The amount of cGMP in

From Texas Tech University Health Science Center, Lubbock, Texas.

**Corresponding author:** Avinash Adiga, MD, Texas Tech University Health Science Center, 3601 4th Street, Lubbock, TX 79430 (e-mail: avinash.adiga@ttuhsc.edu).



**Figure 1.** (a) Computed tomography demonstrating a subarachnoid hemorrhage. (b) Computed tomography angiography showing an anterior carotid artery aneurysm.

cerebrovascular smooth muscles is affected by nitric oxide and PDE. Nitric oxide activates guanylate cyclase in the cerebral arterial cells. The activated guanylate cyclase converts guanosine triphosphate to cGMP. The latter causes relaxation of vascular smooth muscle cells in the cerebral vasculature (9, 10).

The relationship between intracranial hemorrhage (ICH) and sildenafil use is likely due to increased blood flow to the intracranial vessels, which is significantly increased during sexual intercourse. Increased blood flow to the cerebral blood vessels facilitates rupture of the cerebrovascular vessels in patients with other hemorrhagic risk factors (3). Ballard et al suggested that sildenafil also acts on PDE-1 and PDE-2, which are involved in controlling cerebral circulation (11). Studies on mice have demonstrated that sildenafil decreases cerebral vasospasm by increasing and restoring cGMP levels (12). The reported adverse effects of sildenafil include headache, visual disturbances, pupil-sparing third nerve palsy, and transient hypertension, and these symptoms suggest that sildenafil also affects brain microvasculature regulation (13, 14). Unusual susceptibility to this drug could lead to abnormal vasodilatation of cerebral arteries and abnormal redistribution of arterial blood flow in the brain.

The hypothetical relationship between ICH and sildenafil ingestion is not well understood (2, 5). Transcranial Doppler

studies have shown that sildenafil increases cerebrovascular reactivity and causes vasodilation with increased blood flow and volume (15). The vasodilatory effect of sildenafil causes hypotension that could lead to an increase in sympathetic activity, which might be the reason for secondary hypertension leading to SAH, as occurred in our case. Ayberk et al reported a case of intracerebral bleed in a healthy 35-year-old man 3 hours after ingestion of 50 mg of sildenafil without any sexual activity (5). This supports our conclusion that sildenafil results in reactive sympathetic hyperactivity that leads to ICH regardless of the presence or absence of other risk factors, such as hypertension and sexual intercourse. Nevertheless, our known hypertensive patient had an elevated blood pressure and SAH after sildenafil use. Whether the hypertensive crisis in this patient caused by sildenafil was secondary to sympathetic hyperactivity or sexual intercourse or whether the ICH itself caused hypertension cannot be determined. Also, we do not know if there is a dose-related effect which causes ICH. All reported patients ingested 50 mg or more (*Table 1*).

Sildenafil citrate has been shown to be safe in patients without cardiovascular disease but is contraindicated in those with acute coronary syndromes, life-threatening coronary arrhythmias, and recent stroke. The US Food and Drug Administration advises

**Table 1. Reported cases of subarachnoid hemorrhage after sildenafil use**

Variable	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Our case
Age (years)	62	44	62	67	35	49	33	49
Hypertension	Yes	No	Yes	No	No	Unknown	No	Yes
Dose of sildenafil (mg)	50	4 tablets (unknown strength)	50	50	50	Unknown	50	100
Glasgow Coma Scale: admission and discharge	15/15 15/15	15/15/drowsy Deceased	15/15 15/15	15/15 15/15	12/15 15/15	Dead on arrival	3/15 Unknown	Low/intubated 15/15
Type of bleed	Thalamic and capsular	Left temporal	Right subthalamic	Left temporal subcortical	Caudate nucleus	Left ACA, SAH	Right basal ganglia, SAH	Right ACA, SAH

ACA indicates anterior cerebral artery; SAH, subarachnoid hemorrhage. Cases appear in references 1–7.

cautioned use of sildenafil in patients with a history of myocardial infarction or stroke within 6 months and those with resting hypotension, severe hypertension (<170/110 mm Hg), and heart failure (16).

All five previously reported intracerebral hemorrhages with sildenafil use presented with minimal volume hemorrhage in elderly patients with a risk factor of ICH, and surgical evacuation was not required (*Table 1*) (1–5). However, the previous two reports of SAH with sildenafil use were associated with severe bleeding (6, 7). One patient required emergency decompression due to impending herniation, and the other patient was pronounced dead on arrival (6, 7). Our patient rebled following the initial SAH and underwent ventriculostomy and bilateral decompressive craniotomy. His neurological status improved tremendously, and his Glasgow Coma Scale score was 15/15 on discharge. In conclusion, sildenafil is a relatively safe and widely used medication to treat erectile dysfunction. However, serious complications, such as severe ICH and SAH, have been reported with its use.

1. Alpsan MH, Bebek N, Ciftci FD, Coban O, Bahar S, Tuncay R. Intracerebral hemorrhage associated with sildenafil use: a case report. *J Neurol* 2008;255(6):932–933.
2. Buxton N, Flannery T, Wild D, Bassi S. Sildenafil (Viagra)-induced spontaneous intracerebral haemorrhage. *Br J Neurosurg* 2001;15(4):347–349.
3. Martí I, Martí Massó JF. Hemiballism due to sildenafil use. *Neurology* 2004;63(3):534.
4. Monastero R, Pipia C, Camarda LK, Camarda R. Intracerebral haemorrhage associated with sildenafil citrate. *J Neurol* 2001;248(2):141–142.
5. Ayberk G, Ozveren MF, Yaman ME, Tosun H. Intracerebral hemorrhage after sildenafil citrate use: an incidental association? *Urol J* 2014;11(2):1524–1526.
6. Byoun HS, Lee YJ, Yi HJ. Subarachnoid hemorrhage and intracerebral hematoma due to sildenafil ingestion in a young adult. *J Korean Neurosurg Soc* 2010;47(3):210–212.
7. De-Giorgio F, Arena V, Arena E, Arena E, Lodise M, Valerio L, d'Aloja E, Chiariotti M. Subarachnoid hemorrhage during sexual activity after sildenafil intake: an accidental association? *Am J Forensic Med Pathol* 2011;32(4):310–311.
8. McHugh J, Cheek DJ. Nitric oxide and regulation of vascular tone: pharmacological and physiological considerations. *Am J Crit Care* 1998;7(2):131–140.
9. Inoha S, Inamura T, Ikezaki K, Nakamizo A, Amano T, Fukui M. Type V phosphodiesterase expression in cerebral arteries with vasospasm after subarachnoid hemorrhage in a canine model. *Neurol Res* 2002;24(6):607–612.
10. Sobey CG, Quan L. Impaired cerebral vasodilator responses to NO and PDE V inhibition after subarachnoid hemorrhage. *Am J Physiol* 1999;277(5 Pt 2):H1718–H1724.
11. Ballard SA, Gingell CJ, Tang K, Turner LA, Price ME, Naylor AM. Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes. *J Urol* 1998;159(6):2164–2171.
12. Han BH, Vellimana AK, Zhou ML, Milner E, Zipfel GJ. Phosphodiesterase 5 inhibition attenuates cerebral vasospasm and improves functional recovery after experimental subarachnoid hemorrhage. *Neurosurgery* 2012;70(1):178–186.
13. Donahue SP, Taylor RJ. Pupil-sparing third nerve palsy associated with sildenafil citrate (Viagra). *Am J Ophthalmol* 1998;126(3):476–477.
14. Vobig MA, Klotz T, Staak M, Bartz-Schmidt KU, Engelmann U, Walter P. Retinal side-effects of sildenafil. *Lancet* 1999;353(9150):375.
15. Brenner S, Diomedi M, Sallustio F. Sildenafil increases cerebrovascular reactivity: a transcranial Doppler study. *Neurology* 2006;66(9):1455–1456.
16. Kloner RA, Jarow JP. Erectile dysfunction and sildenafil citrate and cardiologists. *Am J Cardiol* 1999;83(4):576–582, A7.

## *Case Studies*

# **Acute Intracranial and Spinal Subdural Hematoma Associated with Vardenafil**

Takaaki Nakamura, MD, Genya Watanabe, MD, Ryuhei Harada, MD,  
Emiko Kawasaki, MD, PhD, Kenichi Tsukita, MD, and Yasushi Suzuki, MD, PhD

---

A 28-year-old healthy man was admitted to our hospital because of right-sided headache, vomiting, and lower back pain after the administration of vardenafil. Computed tomography and magnetic resonance imaging of the brain showed a small, right-sided, subdural hematoma. A lumbar magnetic resonance imaging showed a longitudinally extended subdural hematoma. He had no history of trauma. We speculated that vardenafil might have had an association with the bleeding. Several reports have suggested a relationship between phosphodiesterase-5 inhibitors and intracerebral or subarachnoid hemorrhage. Our case suggested that there may also be risks of bleeding into the subdural space. Although headache and nausea are common side effects of vardenafil, hemorrhagic diseases should also be considered when symptoms are severe or prolonged. **Key Words:** Subdural hematoma—vardenafil—phosphodiesterase-5 inhibitor—spine.

© 2018 National Stroke Association. Published by Elsevier Inc. All rights reserved.

---

### **Introduction**

Phosphodiesterase (PDE)-5 inhibitors, such as vardenafil, are widely used for the treatment of erectile dysfunction. Headache and vomiting are common side effects of PDE-5 inhibitors. Recently, cases of intracerebral and subarachnoid hemorrhages possibly representing the risks and severe adverse effects of PDE-5 inhibitors have been reported.<sup>1-4</sup> We report the case of a healthy young man with intracranial and lumbar, nontraumatic, acute sub-

dural hematoma (ASDH) associated with vardenafil ingestion.

### **Case Report**

A 28-year-old man with no medical history, was admitted after a 3-day history of sudden-onset, right-sided headache with vomiting occurring 2 hours after taking 10 mg of vardenafil. He also noticed lower back pain after the headache onset. He had no history of trauma and his only cardiovascular risk was a 7-year smoking history. He reported having ingested vardenafil solely out of curiosity and denied sexual intercourse. His neurological examination result was nonfocal. Laboratory findings, including platelet count and coagulation panels, were normal. Computed tomography and magnetic resonance imaging (MRI) of the brain revealed a small, right-sided, subdural hematoma (Fig 1, A,B). Magnetic resonance angiography and venography showed no vascular lesions. Lumbar MRI revealed a longitudinally extended subdural hematoma (Fig 1, C,D). His symptoms gradually

---

From the Department of Neurology, National Hospital Organization Sendai Medical Center, Sendai, Japan.

Received February 23, 2018; accepted April 9, 2018.

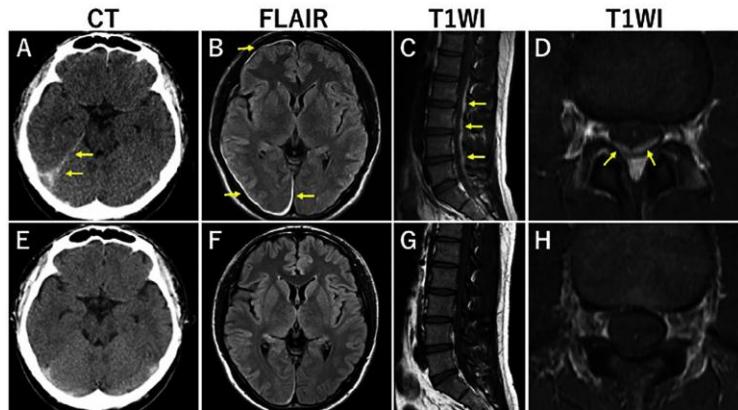
Grant support: Nothing.

Address correspondence to Takaaki Nakamura, MD, Department of Neurology, National Hospital Organization Sendai Medical Center, 2-8-8 Miyagino, Miyagino-ku, Sendai, 983-8520, Japan. E-mail: takaaki@med.tohoku.ac.jp.

1052-3057/\$ - see front matter

© 2018 National Stroke Association. Published by Elsevier Inc. All rights reserved.

<https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.04.006>



**Figure 1.** CT and MRI of the brain in the acute phase and after 1 month. (A) Axial CT views on day 3 demonstrate a right-sided, subdural hematoma along the tentorium cerebelli (arrows). (B) Axial view of FLAIR on day 5 shows a small, right-sided subdural hematoma (arrows). (C and D) Axial and sagittal views of the T1WI on day 10 show a longitudinally extended subdural hematoma (arrows). (E and F) CT and MRI of the brain after 1 month show a decrease in the size of the intracranial subdural hematoma. (G and H) Lumbar MRI after 1 month demonstrates disappearance of the spinal subdural hematoma. Abbreviations: CT, computed tomography; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; T1WI, T1-weighted image.

improved with conservative management, and all symptoms had completely disappeared 10 days after onset. Repeat computed tomography and MRI scans showed decreased intracranial and spinal hematoma sizes (Fig 1, E-H).

### Discussion

To our knowledge, this is the first case of subdural hemorrhage associated with PDE-5 inhibitors. Concomitant intracranial and spinal ASDH are also rare phenomena.<sup>5</sup> A previous study reported a 3% incidence rate for intracranial, nontraumatic ASDH,<sup>6</sup> with risk factors including hypertension, vascular abnormalities such as aneurysm, and anticoagulation therapy.<sup>7</sup> In contrast, similar to other reported cases, our patient had almost no risk factors.<sup>2,4</sup> Although the underlying mechanism remains unknown, the vasodilatory and antiplatelet effects of PDE-5 inhibitors<sup>8,9</sup> may be associated with the ASDH in our patient. Further evidence of the relationship between vardenafil and bleeding in our patient is based on the time from drug ingestion to headache onset, which corresponds to the time to maximum concentration of vardenafil.<sup>10</sup> PDE-5 inhibitors may be associated with intracranial and spinal hematoma risks. When headache, vomiting, and lower back pain appear after the administration of PDE-5 inhibitors, the possibility of hemorrhagic diseases must be considered.

### References

- Bae EK, Ahn JH, Park JJ. Nonaneurysmal subarachnoid hemorrhage after udenafil intake. *J Stroke Cerebrovasc Dis* 2013;22:e647-e649.
- Ayberk G, Ozveren MF, Yaman ME, et al. Intracerebral hemorrhage after sildenafil citrate use: an incidental association? *Urol J* 2014;11:1524-1526.
- Byoun HS, Lee YJ, Yi HJ. Subarachnoid hemorrhage and intracerebral hematoma due to sildenafil ingestion in a young adult. *J Korean Neurosurg Soc* 2010;47:210-212.
- McGee HT, Egan RA, Clark WM. Visual field defect and intracerebral hemorrhage associated with use of vardenafil (Levitra). *Neurology* 2005;64:1095-1096.
- Nagashima H, Tanida A, Hayashi I, et al. Spinal subdural haematoma concurrent with cranial subdural haematoma: report of two cases and review of literature. *Br J Neurosurg* 2010;24:537-541.
- Komatsu Y, Uemura K, Yasuda S, et al. Acute subdural hemorrhage of arterial origin: report of three cases. *No Shinkei Geka* 1997;25:841-845.
- Garbossa D, Altieri R, Specchia FM, et al. Are acute subdural hematomas possible without head trauma? *Asian J Neurosurg* 2014;9:218-222.
- Ballard SA, Gingell CJ, Tang K, et al. Effects of sildenafil on the relaxation of human corpus cavernosum tissue *in vitro* and on the activities of cyclic nucleotide phosphodiesterase isozymes. *J Urol* 1998;159:2164-2171.
- Greselle P, Momi S, Falcinelli E. Anti-platelet therapy: phosphodiesterase inhibitors. *Br J Clin Pharmacol* 2011;72:634-646.
- Bischoff E. Vardenafil preclinical trial data: potency, pharmacodynamics, pharmacokinetics, and adverse events. *Int J Impot Res* 2004;16(Suppl 1):S34-S37.



# A Case of Recurrent Lobar Intracerebral Hemorrhage in the Setting of Phosphodiesterase-5 Inhibitor Use

by Scott A. Lucchese, MD, Arshdeep S. Dhaliwal, MD, Arpanjeet Kaur, MD & Laura Qi, MD

This case bolsters existing evidence that phosphodiesterase-5 inhibitors as a class should be viewed with caution. As of publication, FDA warns against possible cardiovascular adverse reactions, hearing loss, hypotension, and priapism, however does not warn that intracerebral hemorrhage may be possible side effect.



Scott A. Lucchese, MD, (above), MSMA member since 2017, is Associate Professor of Clinical Neurology. Arshdeep S. Dhaliwal, MD, and Laura Qi, MD, are in Clinical Neurology. All are at the University of Missouri-Columbia School of Medicine, Columbia, Missouri. Arpanjeet Kaur, MD, is in the Government Medical College, Patiala, India.  
Contact: [LuccheseS@health.missouri.edu](mailto:LuccheseS@health.missouri.edu)

## Abstract

Intracerebral hemorrhage occurs when a diseased blood vessel within the brain bursts. We present a case of 69-year-old patient with two sequential episodes of lobar intracerebral hemorrhage occurring during sexual intercourse. Both episodes were associated with the use of phosphodiesterase-5 inhibitors. This is the first case reported which is temporally associated with isolated bilateral lobar bleeds with appropriate use of phosphodiesterase-5 inhibitor on two different occasions associated with sexual intercourse.

## Introduction

Intracerebral hemorrhage (ICH) (code 431, International Classification of Diseases, 9th Revision) is a neurological deficit documented by brain CT or MRI showing the presence of an intracranial bleed in the parenchyma of the brain.<sup>1</sup> ICH is a serious cerebrovascular condition associated with high mortality and morbidity in adults. Etiological factors for spontaneous ICH include vasculopathies, such as, cerebral amyloid angiopathy, hypertension, aneurysms, vascular malformations;

alcohol ingestion; coagulopathies; drugs; tumors; and genetics.<sup>2-4</sup> The risk of lobar ICH significantly increases with age, as well<sup>5</sup>.

Oral phosphodiesterase-5 inhibitors are commonly used for the treatment of erectile dysfunction (ED). These medications are also thought to be possibly beneficial for treatment of cerebrovascular and pulmonary diseases. Sildenafil, a phosphodiesterase-5 inhibitor, has an expanding role in the treatment of pulmonary hypertension.<sup>6</sup> Common side effects include flushing, headache, nasal congestion, changes in pulmonary blood flow and ischemic manifestations, such as transient ischemic attack, ischemic stroke, cerebral infarction, or ischemic optic neuropathy. Since the approval of these medications in 1998, multiple reports have tied their use, both appropriate and inappropriate, to ICH and retinal hemorrhages.<sup>2,7-20</sup>

We present a 69-year-old male with clinical and radiological evidence of two (right and left frontal) incidences of lobar ICH occurring on two separate occasions during sexual intercourse, both associated with appropriate use of phosphodiesterase-5 (PDE-5) inhibitor for erectile dysfunction.

**Case Report: History and Clinical Findings**

The patient was a 69-year-old white male who experienced two episodes of intracranial lobar hemorrhage temporally associated with PDE-5 use. He had previous history of intracerebral hemorrhage nine months prior to presentation, coronary artery disease, colon cancer status post two resections, and subsequent chemo and radiation therapy, erectile dysfunction and hyperlipidemia. He presented to the emergency department with complaints of one-day history of headache, confusion, and inability to concentrate. The headache was bifrontal in location without radiation, 5/10 in intensity and squeezing in character. There was no associated photophobia, phonophobia, nausea, congestion or lacrimation. There was no slurring of speech, hearing loss, neck stiffness or significant weakness. The patient has been normotensive and non-diabetic throughout his life. He was on multi-vitamin, 81 mg aspirin, sildenafil (25mg) for his erectile dysfunction, and tamsulosin for benign prostatic hyperplasia.

He had strong family history of coronary artery disease and myocardial infarction. He had a daughter with brain aneurysm which was treated surgically. He did not smoke, drink, or use illicit drugs. His labs were within normal range without abnormal platelet count or INR.

On examination, he was well nourished and in no acute distress. The remainder of the general examination was unremarkable. On mental status exam he scored 12/30 on MMSE with deficits in all spheres except repetition and orientation to place. His executive functions were compromised with difficulty calculating and was also not able to follow three step commands. He was not able to repeat three objects consecutively and follow written commands. In addition, he had verbal and action perseveration. The remainder of the cranial nerve exam was unremarkable.

Motor exam was unremarkable. Deep tendon reflexes were symmetric. Sensation to all modalities was intact. He had no ataxia. Cortical sensations including graphesthesia and stereognosis were normal.

On fundoscopic exam, the patient had bilateral papilledema. The patient was hypertensive (160/90mmHg) and required intravenous (IV) hydralazine for control of blood pressure. While in the emergency department his headache resolved a few hours after presentation. He was started in emergency department on phenytoin for seizure prophylaxis after ICH.

Non-contrast computed tomography (CT) of brain showed acute left frontal lobe bleed and chronic right frontal encephalomalacia from prior ICH (Figure 1). About nine months prior to current presentation, he had presented with a similar syndrome and brain CT at that time showed large right frontal bleed (Figure 2—the remnant of this bleed is the source of chronic changes in Figure 1). Head Magnetic Resonance Imaging (MRI) exam showed a left frontal intracerebral hemorrhage with both a subacute and acute component with minimal mass effect on left lateral ventricle and no midline shift. The MRI was also notable for evidence of previous right frontal hemorrhage, mostly resolved, with resultant encephalomalacia. Periventricular T2 hyperintense signals were present in the frontal areas suggesting chronic small vessel disease (SVD) (see Figure 3 current bleed, Figure 4 for prior right bleed). Carotid duplex ultrasound demonstrated mild carotid plaques bilaterally without any significant stenosis. MRA angiogram of head and neck were negative for any aneurysm, arteriovenous malformations or other vascular anomalies.

On further discussion with the patient's wife on the second day of the admission, she noted that the patient's headache began while they were engaged in sexual intercourse. She also noted they had been engaged in intercourse leading up to the previous episode of ICH approximately nine months prior when the patient had the initial right sided frontal intralobar hemorrhage (Figure 4). She noted the prior headache occurred during intercourse while using tadalafil for erectile dysfunction. She also noted he had taken sildenafil (25mg) and was engaged in intercourse just prior to development of the headache which led to the current presentation, and discovery of the new left intralobar frontal hemorrhage (Figure 3).

The temporal relationship of the two occurrences of ICH on two different occasions with the use of the PDE-5 inhibitors was concerning for possible causality. It seems likely that type PDE-5 inhibitor use and sexual activity in the setting of underlying vascular pathology, possibly amyloid angiopathy, contributed to the bleeds. He had used PDE-5 inhibitors several other times in the past, but not with a great deal of frequency. The wife could not give a detailed history of this and the patient wasn't aware at that point and time how often he had used them. He never reported a sexual headache prior to his first presentation of ICH. He was counseled to stop taking any

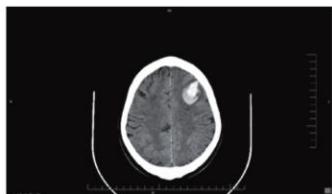


Figure 1. Computed tomography of brain showing second episode of left frontal bleed and right frontal encephalomalacia from the first episode.



Figure 2. Computed tomography of brain showing first episode of large right frontal bleed.

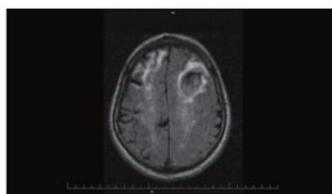


Figure 3. FLAIR image with second episode of acute bleed in left frontal lobe and sequela of prior bleed with gliosis in right frontal region.

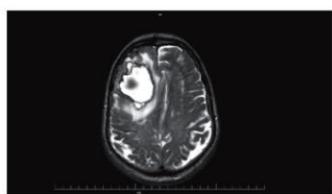


Figure 4. First episode of right acute frontal bleed with edema and mild midline shift; diffuse T2 signal hyper-intensity in the periventricular region consistent with small vessel disease.

PDE-5 inhibitors after his second episode. Unfortunately, he was not advised to discontinue use of PDE-5 inhibitors after his first episode of intracerebral hemorrhage.

The patient did well initially with conservative management after both bleeds. His phenytoin was discontinued at discharge. Approximately eighteen months after the second bleed, he developed partial complex epilepsy and was treated with levetiracetam which he tolerated very well. He had to give up his real estate business due to his executive dysfunction resulting from the bilateral bleeds.

### Discussion

The overall incidence of intracerebral hemorrhage (ICH) is 12 to 15 cases per 100,000 individuals or about 40,000 cases per year in the United States. Spontaneous (atraumatic) primary ICH is a catastrophic form of stroke associated with high morbidity and mortality

and a substantial recurrence risk. Lobar ICH location is associated with the risk of subsequent ICH recurrence, likely because of the type and severity of the underlying small vessel diseases (microangiopathies), which include arteriolosclerosis, lipohyalinosis, and cerebral amyloid angiopathy (CAA).<sup>18</sup>

Intracerebral hemorrhage mortality is about 40% at 30 days, similar to SAH in acute mortality.<sup>3</sup> The five-year mortality rate is over 50% (52% for males, 56% for females) in ICH patients older than 45 years, and the 10-year survival rate is 24.1%.<sup>1,11</sup> For those who survive a spontaneous ICH, the risk of recurrence is in the 2% range, annually.<sup>1</sup> Since our patient was normotensive and non-diabetic, it is highly suspicious that amyloid deposition might have played a significant role in altering the microstructure of the cerebral vessels.

Fourteen cases of adult intracranial hemorrhage associated with the use of PDE-5 were found on review of the English language literature. The case reports' subjects range from 33 years old to 70 years old. All developed cerebral hemorrhage symptoms (including headache, dizziness, blurry vision, decreased mentation, and nausea) 30 minutes to three hours after ingestion of PDE-5 inhibitor. None of these subjects had history of ICH. One report noted the patient described was found to have an arterial venous malformation, which was thought to be the cause of the hemorrhage.<sup>20</sup> None of the other cases reported known vascular malformations. Bleed location varied from cortical to subcortical without any appreciable correlation to age of subjects. Dosage varied from appropriate to excessive, but it remains unclear what the degree of dose related risk of ICH is associated with PDE-5 use.<sup>2,7-10,12,13,15,17-19,21-24, 25</sup>

The relationship between ICH and PDE-5 inhibitors is likely due to increased blood flow to the intracranial vessels during sexual intercourse which is further enhanced by concurrent use of these drugs. Sexual intercourse is known to produce a hyper dynamic circulatory state in both men and women, manifested by increased heart rate and blood pressure.<sup>7,15</sup> Following sexual stimulation, penile erection occurs through the release of nitric oxide (NO), which causes dilation of the blood vessels of the corpus cavernosum via an accumulation of cyclic guanosine monophosphate (cGMP). The PDE-5 inhibitors enhance this vasodilatory effect of NO-cGMP pathway by inhibiting PDE-5, the enzyme responsible for breakdown of cGMP. Studies have

also shown that sildenafil acts on phosphodiesterase-1, -2 and -5 receptors and leads to a secondary increase in intracerebral circulation and vasodilatory effects, leading to sympathetic over activity which increases the risk for intracranial bleeding.<sup>25,26</sup> Side effects of sildenafil, including flushing, headache, nasal congestion, and changes in pulmonary blood flow indicate the multisystem vasodilation caused by these drugs.<sup>27,28</sup>

Our case appears to be first one highlighting the temporal relationship between usage of two separate PDE-5 inhibitors and two separate episodes of ICH in different areas of the brain in one patient. This case bolsters existing evidence that PDE-5 inhibitors as a class should be viewed with caution. As of publication, FDA warns against possible cardiovascular adverse reactions, hearing loss, hypotension, and priapism, however does not warn that ICH may be possible side effect.

### Conclusion

This case of recurrent lobar hemorrhages revolves around use of PDE-5 inhibitors and ICH likely associated with preexisting microvasculature pathology, precipitating ICH. It illustrates the risk of intracranial hemorrhage associated with the use of PDE-5 inhibitors during sexual intercourse. It would appear to be a particularly cautionary tale in the instance of prior intracranial bleed, or in the setting of known cerebrovascular disease. It is of utmost importance to discuss the risks and benefits before prescribing such medications to patients with possible underlying vasculopathies and/or prior bleed. If it is desirable to use these medications, it is likely prudent to start at the lowest possible dose in these populations.

### References

1. Aguilar MI, Brott TGJTN. Update in intracerebral hemorrhage. 2011;1:148-59.
2. Buxton N, Flannery T, Wild D, Bassi S. Sildenafil (Viagra)-induced spontaneous intracerebral haemorrhage. Br J Neurosurg 2001;15:347-9.
3. Aguilar MI, Brott TG. Update in Intracerebral Hemorrhage. The Neurohospitalist 2011;1:148-59.
4. Caceres JA, Goldstein JN. Intracranial Hemorrhage. Emergency Medicine Clinics of North America 2012;30:771-94.
5. Skidmore CT, Andrefsky JJNCoNA. Spontaneous intracerebral hemorrhage: epidemiology, pathophysiology, and medical management. 2002;13:281-8, v.
6. Barnett CF, Machado RFVh, management r. sildenafil in the treatment of pulmonary hypertension. 2006;2:411.
7. Abramson DH, Rollins IS, Lin A, Odell P, Folberg R. tadalafil-induced subretinal and choroidal hemorrhage in a patient with an unsuspected uveal (choroidal and ciliary body) melanoma. Archives of Ophthalmology 2006;124:1058-60.
8. Alsan M, Bebek N, Ciftci F, Coban O, Bahar S, Tuncay R. Intracerebral hemorrhage associated with sildenafil use: a case report. Journal of neurology 2008;255:932-3.
9. Antar V, Koksal Sutpideler NH, Baran O, Bitirak G. Subarachnoid and intracerebral hemorrhage after alcohol ingestion and illicit use of sildenafil. 2014.
10. Bae E-K, Ahn J-H, Park J-J. Nonaneurysmal Subarachnoid Hemorrhage after Udenafil Intake. 2013;22:e647-e9.
11. Byoun H-S, Lee Y-J, Yi H-J. Subarachnoid hemorrhage and intracerebral hematoma due to sildenafil ingestion in a young adult. Journal of Korean Neurosurgical Society 2010;47:210-2.
12. De-Giorgio F, Arena V, Arena E, et al. Subarachnoid hemorrhage during sexual activity after sildenafil intake: an accidental association? 2011;32:310-1.
13. Gazzera R, Neroni M, Galarza M, Esposito S. Intracerebral hemorrhage associated with use of tadalafil (Cialis). Neurology 2008;70:1289-90.
14. Hellstrom WJG, Egan RA, McGee HT, Clark WM. Visual field defect and intracerebral hemorrhage associated with use of vardenafil (Levitra). 2006;66:293-4.
15. Kaneria MV, Pagar S, Samant H, Yeole S, Patil SJ. Subarachnoid haemorrhage: possibly caused by the illegitimate use of sildenafil citrate. 2008;56.
16. Monastero R, Pipia C, Camarda LK, Camarda R. Intracerebral haemorrhage associated with sildenafil citrate. J Neurol 2001;248:141-2.
17. Nakamura T, Watanabe G, Harada R, Kawasaki E, Tsukita K, Suzuki Y. Acute Intracranial and Spinal Subdural Hematoma Associated with Vardenafil. Journal of Stroke and Cerebrovascular Diseases 2018;27:e201-e2.
18. Ozveren MF, Yaman ME, Tosun HJUj. Intracerebral hemorrhage after sildenafil citrate use: an incidental association? 2014;11:1524-6.
19. Sheikh-Taha M, Alawy RAJAjoH-SP. Subarachnoid hemorrhage associated with tadalafil. 2011;68:1195-6.
20. Steeves TD, Jones LK, Ecker RD, Manno EM. Coital hemorrhage of an arteriovenous malformation after premedication with tadalafil (Cialis). Journal of Stroke and Cerebrovascular diseases 2005;14:179-81.
21. Byoun H-S, Lee Y-J, Yi H-J, KNS. Subarachnoid hemorrhage and intracerebral hematoma due to sildenafil ingestion in a young adult. 2010;47:210.
22. McGee HT, Egan RA, Clark WM. Visual field defect and intracerebral hemorrhage associated with use of vardenafil (Levitra). Neurology 2005;64:1095-6.
23. Monastero R, Pipia C, Camarda LKC, Camarda R. Intracerebral haemorrhage associated with sildenafil citrate. 2001;248:141-2.
24. Steeves TDL, Jones LK, Ecker RD, Manno EM. Coital Hemorrhage of an Arteriovenous Malformation after Premedication with tadalafil (Cialis). 2005;14:179-81.
25. Adiga A, Edriss H, Nugent K. Intracranial aneurysm and sildenafil. Baylor University Medical Center Proceedings; 2016: Taylor & Francis. p. 178-80.
26. Xue-Rui T, Ying L, Da-Zhong Y, Xiao-Jun C. Changes of blood pressure and heart rate during sexual activity in healthy adults. 2008;13:211-7.
27. Morales A, Gingell C, Collins M, Wicker P, Osterloh I. Clinical safety of oral sildenafil citrate (VIAGRATM) in the treatment of erectile dysfunction. International Journal of Impotence Research 1998;10:69-73.
28. Morgan JC, Alhatou M, Oberlies J, Johnston KC. Transient ischemic attack and stroke associated with sildenafil (Viagra) use. Neurology 2001;57:1730-1.

### Disclosure

None reported.

**MM**

**DAVID DEARINGER - FILING PRO SE**

**September 13, 2021 - 9:06 AM**

**Transmittal Information**

**Filed with Court:** Supreme Court

**Appellate Court Case Number:** 99956-2

**Appellate Court Case Title:** David J. Dearinger et al. v. Eli Lilly Company

**The following documents have been uploaded:**

- 999562\_Briefs\_20210913090207SC975553\_9340.pdf  
This File Contains:  
Briefs - Other  
*The Original File Name was 99956-2\_Dearinger v. Lilly.pdf*

**A copy of the uploaded files will be sent to:**

- AppellateAssistants@schwabe.com
- Ksmith@schwabe.com
- atalcott@schwabe.com

**Comments:**

Petitioner's Obening Brief on Certified Question

---

Sender Name: David Dearinger - Email: daviddearinger@comcast.net

Address:

10218 38th Pl SE  
Lake Stevens, WA, 98258-5738  
Phone: (425) 220-3690

**Note: The Filing Id is 20210913090207SC975553**