IN THE SUPREME COURT

STATE OF NORTH DAKOTA

No. 20130259

MKB Management Corp. d/b/a/ Red River Women's Clinic, Tammi Kromenaker, Kathryn L. Eggleston, M.D.,

Plaintiffs-Appellees,

v.

Birch Burdick, in his official capacity as State Attorney for Cass County,

Defendant,

Terry Dwelle, M.D., in his official capacity as the chief administrator of the North Dakota Department of Health,

Defendant-Appellant.

Appeal from Memorandum Opinion and Order for Permanent Injunction entered in Cass County, East Central Judicial District
The Honorable Wickham Corwin (No. 09-2011-cv-02205)

AMICUS CURIAE BRIEF AND ADDENDUM OF NORTH DAKOTA MEDICAL ASSOCIATION IN SUPPORT OF APPELLEES AND IN SUPPORT OF AFFIRMANCE

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STATEMENT OF IDENTITY AND INTEREST OF *AMICUS CURIAE*

Founded in 1887, the North Dakota Medical Association is the professional membership association for active and retired physicians, residents, and medical students in North Dakota. The Association's membership is comprised of more than 1,600 members who represent all medical specialties and all practice settings in the State. The mission of the Association is to promote the health and well-being of the citizens of North Dakota and to provide leadership to the medical community.

The North Dakota Medical Association's interest in this case is in protecting the primacy of the medical judgment of its members in advising North Dakotans about medical decisions. Further, the Association strongly objects to the inappropriate importation of an inapplicable FDA regulatory regime into the law at issue. The Association respectfully submits that its expert views as a body of trained medical professionals may be of assistance to the Court as it considers the important medical questions and policies at issue in this dispute.*

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* No party's counsel authored the brief in whole or in part; no party or party's counsel contributed money that was intended to fund preparing or submitting the brief; and no person, other than the *amicus curiae*, its members, or its counsel, contributed money that was intended to fund preparing or submitting the brief.

ARGUMENT

The North Dakota Medical Association, based on the training and experience of its members, raises two objections to the legislation at issue in this appeal ("the Act"). See H.B. 1297, 62d N.D. Legis. Sess. (2011). First, the Act intrudes on the private relationships between North Dakotans and their physicians, to the determent of those relationships and the health and safety of patients. Second, the Act inappropriately invokes the Food and Drug Administration's marketing approval process in its mandates and requires physicians to violate prevailing standards of care and good medical judgment. These objections rest on the Association's profound concern for the health and well-being of its members' patients, rather than any particular ideological view regarding the social issues implicated by the Act. The Association respectfully submits this brief to inform the Court about the risks and dangers of countenancing the policies the Act embodies. The Association thus urges the Court to affirm the District Court's judgment.

I. The Act Intrudes on the Private Relationships Between North Dakotans and Their Physicians.

Reproductive healthcare is a private matter between patient and physician. Safe and effective healthcare regarding such a personal topic depends on a strong patient-physician relationship. The North Dakota Medical Association supports affirmance in this case to protect that relationship from government intrusion. The

Act represents unsound and dangerous medical policy, and the District Court's order enjoining its enforcement should be affirmed.

The Act intrudes on the patient-physician relationship in three concrete ways. First, following the Act's treatment protocol, a physician is required to administer three times more medication than a patient needs. Second, the physician is required to instruct the patient to appear at the clinic during a time when it is safer for the patient to remain at home. Third, the physician is required to give the patient erroneous and dangerous instructions regarding what the patient should do if she experiences a medical emergency. All of these intrusions force a physician to violate prevailing standards of medical care and good medical judgment.

Last year, the North Dakota Medical Association expressed its strong disapproval of and policy against "interference by the government and third parties that causes a physician to compromise his or her medical judgment as to what information or treatment is in the best interest of the patient."[1] Specifically, the Association opposes laws "that interfere with the patient-physician relationship or that prevent physicians from freely discussing with, or providing information to, patients about medical care and procedures, or which direct physicians to provide specified information or perform specified tests that are not medically

[1] Protecting The Patient-Physician Relationship, N.D. Med. Ass'n House of Delegates Res. 4 (Oct. 22, 2012).

necessary."[2] Such laws "put physicians in an untenable position of risking disciplinary proceedings or criminal prosecution" and "interfere with patient safety and with the patient's ability to have access to adequate medical information."[3]

In addition to North Dakota's physicians, many national physician organizations have objected to legislative intrusion into the physician-patient relationship. For example, representatives of the American Academy of Family Physicians, the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, the American College of Physicians, and the American College of Surgeons wrote to the New England Journal of Medicine to object to a rising tide of laws that "inappropriately infringe on clinical practice and patient-physician relationships, crossing traditional boundaries and intruding into the realm of medical professionalism."[4] These laws relate to a wide range of medical care, including preventive medicine, end-of-life decision-making, exposure to potential carcinogens, and family planning.[5] This is harmful because "[l]egislative mandates regarding the practice of medicine do not allow for the infinite array of exceptions—cases in which the mandate may be unnecessary,

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[2] Id.

[3] Id.

[4] Steven E. Weinberger, M.D., et al., Legislative Interference with the Patient-Physician Relationship, 367 New Eng. J. Med. 1557, 1557 (2012).

[5] Id. at 1557-58.

inappropriate, or even harmful to an individual patient."[6] If this Court does not recognize the importance of the relationships between North Dakota physicians and their patients, it will give tacit approval to erosion of this relationship on any number of topics and in any number of ways.

It is a common misconception that legislative mandates regarding medical care and practice are limited to the realm of reproductive healthcare. In fact, in recent years, legislatures across the nation have seen fit to impose a variety of mandates on their state's physicians that intrude into the traditionally private relationship between physicians and their patients. These laws have prompted physicians to object to the emerging trend, regardless of their individual views on the social issues implicated by such laws.[7]

The American College of Physicians (ACP) recently cataloged examples of these laws and articulated the deleterious effects they have on the ethical practice of medicine and the protection of patients' autonomy.[8] Examples abound from areas of medicine dissimilar to that at issue in this case. In one state, proposed legislation would have invalidated do-not-resuscitate orders and required them to be reconsidered in accordance with a government-mandated regime.[9] In other states, physicians are required by law to provide inaccurate information about

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[6] Id. at 1558.

[7] American College of Physicians, Statement of Principles on the Role of Governments in Regulating the Patient-Physician Relationship (July 2012).

[8] Id.

[9] Id. at 3.

mammograms.[10] Another law imposes criminal penalties on physicians who do not have an end-of-life planning conversation with their patients in a government-approved manner.[11] These laws "inappropriately infringe on clinical medical practice and patient-physician relationships . . . and could compromise patient safety."[12] In response, the ACP has adopted principles, which provide, in pertinent part, that "[p]atients should not be required to undergo tests or interventions, especially invasive and potentially harmful interventions, that violate the patient's values, are not medically necessary, and are not supported by scientific evidence on clinical effectiveness or could expose the patient to unnecessary risk, and physicians should not be required to provide such services."[13]

In this case, if the Act is given effect, three concrete intrusions into the patient-physician relationship will become law. First, following the Act's treatment protocol, a physician would be required to administer medications in a manner inconsistent with prevailing clinical practice. The protocol mandates that a physician administer three times an appropriate dose of a medication via a clinically inappropriate route. Second, a physician is required to instruct his or her patient to present herself at a clinic for an appointment that is not clinically

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[10] Id.

[11] Id. at 5.

[12] Id. at 2.

[13] Id. at 7.

necessary or advisable. Third, the physician is required to erroneously inform a patient that, in the event of an emergency, the patient should take actions other than seeking care at the closest appropriate hospital. All of these intrusions force a physician to violate prevailing standards of medical care and good medical judgment. They invade the physician-patient relationship because patients cannot be sure that their physicians are prioritizing patient needs, as opposed to extraneous legal mandates. Sound clinical practice rests on a physician's deep knowledge of the medical sciences honed over years of training and experience. This Court should uphold a physician's ability to accurately convey and implement that knowledge to advise a patient in medical decision-making.

The medical techniques and protocols at issue in this case are the subject of ongoing scholarly research and discourse. This discourse belongs in medical journals and schools, not in the state house or the courthouse. This discourse results in judgments that belong in the hands of physicians informed by professional enquiry, education, and experience, not in the hands of law-makers, all too often driven by politics, partisanship, and pandering. And in North Dakota's hospitals, clinics, and homes, when this discourse meets reality as a patient decides on a course of treatment with a physician's guidance, there is no room for governmental intrusion. Because if laws like the Act crowd physicians and patients out of the exam room, patients will go elsewhere. The risks of

turning elsewhere, where there are no physicians, have been documented for generations.[14] Those risks are mortal.[15]

II. The Act Inappropriately Invokes the Food and Drug Administration's Marketing Approval Process in its Mandates.

The marketing, sale, and use of prescription medications in the United States are the subjects of a complex web of federal and state statutes, regulations, and oversight. The U.S. Food & Drug Administration (FDA) plays a prominent, but by no means exclusive role, in this web. The Act ham-handedly invokes the FDA's role by incorporating the FDA's medication marketing approval process, which the Act claims produces a "document that delineates how a drug is to be used according to the federal food and drug administration [sic]." H.B. 1297 § 1, 62d N.D. Legis. Sess. (to be codified at N.D.C.C. § 14-02.1-02). The Act misconstrues the document at issue, the FDA's role in its creation and distribution, and its meaning and effect in the practice of medicine.

The North Dakota Medical Association opposes the legislature's invocation of the FDA's marketing approval process in structuring the Act. The District Court found that the Act, by incorporating the FDA's approved marketing materials, required a 600 milligram dose of Mifeprex despite that it is the

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[14] Phillip G. Stubblefield, M.D., & David A. Grimes, M.D., Septic Abortion, 331 New Eng. J. Med. 310, 310-14 (1994).

[15] J.A. Presley, M.D., & W.E. Brown, M.D., Lysol-Induced Criminal Abortion, 8 Obstetrics & Gynecology 368, 368-370 (1956).

universally recognized standard of care to administer only 200 milligrams.[16] (A. 179.) Unnecessarily exposing women to a higher dosage of medication may result in increased patient side effects including nausea, vomiting, diarrhea, among others. The increased dosage increases the cost of the procedure by at least $170 at a clinic where approximately 40% of the patients fall below the federal poverty level. (A. 179.) The District Court also found that the Act requires that the route and dosage of the second medication, misoprostol, vary from the standard of care. (A. 180.) It found that most of the clinic's patients travel long distances; about two-thirds travel more than two hours one-way. (A. 181.) Thus, if the Act's requirement that a patient make a third, unnecessary trip to the clinic is followed, most of the clinic's patients "will experience the process of expulsion in a car, rest stop, or some equally inappropriate and discomfiting location." (A. 182.)

The District Court based its decision on its findings of fact after a full trial in Cass County. (A. 154-202.) It explicitly found that the State's sole scientific expert was not credible. (A. 167.) Further, it found that the Red River Women's Clinic served an "extensive geographic area," which meant that imposing a protocol requiring a third trip to the clinic to complete the procedure would be especially burdensome on its patients. (A. 183.) These findings, and many others, are specific to this clinic in this State.

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[16] The District Court also appropriately found that, as written, the Act amounted to a complete procedural ban, which is objectionable simply because it denies patients access to a constitutionally-protected medical procedure. (A. 176.)

As a result, the recent decision of a federal trial court in Texas should not guide the Court in this case. See Planned Parenthood of Greater Tex. Surgical Health Servs. v. Abbott, No. 1:13-CV-862, 2013 WL 5781583, at *7-11 (W.D. Tex. Oct. 28, 2013). In Planned Parenthood, the Texas court ultimately held that, as to a new Texas statute, "the medication-abortion provisions may not be enforced against any physician who determines, in appropriate medical judgment, to perform a medication-abortion using the off-label protocol for the preservation of the life or health of the mother." Id. at *11.[17] The Texas court thus, applying federal law, did not extend its holding to invalidate the forced-adherence to the "FDA protocol" in all cases, as the District Court did in this case after making its findings of fact. See id.

It is axiomatic that this Court does "not reweigh the evidence or reassess credibility when there is evidence to support a district court's findings." Dvorak v. Dvorak, 2006 ND 171, ¶ 11, 719 N.W.2d 362. This Court "will not reverse a district court's decision merely because we might have reached a different result." Id. This Court "will not retry a case; if there is reasonable evidence in the record to support the district court's decision, we will affirm." Ramstad v. Biewer, 1999 ND 23, ¶ 18, 589 N.W.2d 905. Further, the State has expressly waived any objections to the District Court's findings of fact (Br. at 3), making it appropriate

[17] Notably, a subsequent appellate court order granting a stay pending appeal merely modified this portion of the trial court's decision. See Planned Parenthood of Greater Tex. Surgical Health Servs. v. Abbott, No. 13-51008, 2013 WL 5857853, at *6-9 (5th Cir. Oct. 31, 2013).

to affirm those findings in this case, see Weeks v. N.D. Workforce Safety & Ins. Fund, 2011 ND 188, ¶ 8, 803 N.W.2d 601, including any findings that may be contrary to findings of other courts in other states deciding other cases.

The State repeatedly refers to the Act's prescriptions as the "FDA-approved protocol." (See Br. at 20.) This mischaracterization is based on the statute, which erroneously claims that the FDA has created a "document that delineates how a drug is to be used." H.B. 1297 § 1. The District Court found this characterization flawed in that the FDA's approval of marketing materials "does not define medical standards of care or impose any restrictions on the practice of medicine." (A. 177.) Further, medically-appropriate use that diverges from the marketing materials "is neither prohibited nor discouraged by the FDA." (A. 178.)

The amicus brief of forty-nine legislators perpetuates the Act's inaccuracy, claiming that the statute "simply requires that the regimen be administered in the way deemed safest by the FDA." (Br. at 2.) This misapprehension of federal food and drug law illustrates the fundamental problem with invoking the FDA's marketing approval process in a state medical restriction statute—the two are not intended to achieve the same ends. Melding the two conflates unrelated issues. The legislators call it the "the FDA-approved protocol" (Br. at 12) and later claim that "adequate alternatives exist for women who are past the 49-day gestational limit imposed by the FDA" (Br. at 18 (emphasis added)). Neither of these characterizations reflects reality.

The FDA does not "approve" protocols for use in clinical practice; rather, the FDA approves marketing materials when a medication is introduced to the market. (A. 177.) The approved marketing materials are static in that they do "not provide any information regarding advances in the relevant medical sciences" since the experiments upon which they are based were performed. (A. 177.) Using medications in ways not contemplated by the approved marketing materials is referred to as "off-label" usage. N.D.C.C. § 26.1-36-06.1(1)(c).

"Off-label" use of medication is a routine and medically appropriate practice protected by North Dakota and federal law. North Dakota has recognized the importance of protecting appropriate off-label use of prescription medication. See N.D.C.C. § 26.1-36-06.1. State law prohibits an insurance company from refusing to pay for off-label use of a medication so long as the use is recognized in "standard reference compendia or medical literature." Id. § 26.1-36-06.1(2). This sensible prohibition is consistent with federal law, which also recognizes the primacy of physician decision-making concerning the use of approved medications. The FDA has recently and specifically reaffirmed its long-standing recognition that off-label usage is appropriate.[18] According to the FDA, "[o]nce a product has been approved for marketing, a physician may prescribe it for uses or

[18] U.S. Food and Drug Administration, "Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices - Information Sheet," http://www.fda.gov/regulatoryinformation/guidances/ucm126486.htm (Aug. 10, 2011); U.S. Food and Drug Administration, Use of Approved Drugs for Unlabeled Indications, FDA Drug Bull., Apr. 1982, at 4-5.

in treatment regimens or patient populations that are not included in approved labeling."[19] Further, "[t]he term 'unapproved uses' is, to some extent, misleading" because "accepted medical practice often includes drug use that is not reflected in approved drug labeling," and "[w]ith respect to its role in medical practice, the package insert is informational only."[20]

Drug manufacturers have a diminished incentive to pursue formal modification of approved medication labels because off-label use is legally sound and medically appropriate.[21] Therefore, according to the American Society of Health-System Pharmacists, "a product's labeling sometimes fails to represent the most current therapeutic information for a drug, and situations naturally occur when it is appropriate to prescribe drugs for unlabeled uses."[22] Nevertheless, "[t]he prescribing, dispensing, and administration of FDA-approved drugs for uses, treatment regimens, or patient populations that are not reflected in FDA-approved product labeling often represent a therapeutic approach that has been extensively studied and reported in medical literature."[23] That is why off-label usage is "not indicative of inappropriate usage."[24]

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[19] Use of Approved Drugs for Unlabeled Indications at 5.

[20] Id.

[21] American Society of Hospital Pharmacists, ASHP Statement on the Use of Medications for Unlabeled Uses, 49 Am. J. Hosp. Pharm. 2006, 2006-08 (1992).

[22] Id.

[23] Id.

[24] Id.

The Act's invocation of the FDA's marketing approval practice rests on the false premise that the FDA has "approved" the mechanism of usage described in those marketing materials. The FDA's role, purpose, and statutory mandate do not serve this end. Arguing otherwise is analogous to claiming that when a District Court probates a will, it "approves" the decedent's decision to leave his possessions to his favorite charity and requires all others to do the same, forever.

The Act's required adherence to an outmoded protocol for administration of the drugs at issue is especially egregious because it forces North Dakota's physicians to administer three times the clinically appropriate dose of Mifeprex. It forces physicians to set aside their medical knowledge, training, and experience and practice medicine in a manner not consistent with the prevailing standard of care. The Act thus compels a physician to violate his or her oath to "serve the highest interests of my patients through the practice of my science and my art."[25]

CONCLUSION

For the foregoing reasons, the *amicus curiae* North Dakota Medial Association respectfully requests that this Court affirm the District Court's judgment.

[25] Weill Cornell Medical College, Hippocratic Oath (2005).

Dated this 7th day of November, 2013.

Respectfully submitted,

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By _____

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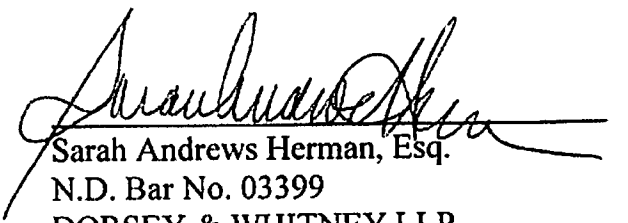
CERTIFICATE OF COMPLIANCE

I certify that this *Amicus Curiae* Brief complies with the type-volume limitation of the N.D. R.App.P. 32 and N.D.R.App.P 29 because it contains only **3,286** words, excluding parts of the brief exempted by the rules. I relied on my word processor, Microsoft Word 2010, to obtain the count.

I further certify that this *Amicus Curiae* Brief complies with the typeface requirements of N.D.R.App.P. 32 because it has been prepared in a proportionally-spaced typeface using Microsoft Word 2010 in Times New Roman font, size 13.



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Terry Dwelle, M.D., in his official capacity as the chief administrator of the North Dakota Department of Health,

Defendant-Appellant.

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Gail Smith states under oath as follows:

1. I swear and affirm under penalty of perjury that the statements made in this affidavit are true and correct.

2. I am of legal age and on the 8th day of November, 2013, I served a true and correct copy of the attached **NORTH DAKOTA MEDICAL ASSOCIATION'S MOTION FOR LEAVE TO FILE AMICUS CURIAE BRIEF AND ADDENDUM OF NORTH DAKOTA MEDICAL**

ASSOCIATION IN SUPPORT OF APPELLEES AND IN SUPPORT OF AFFIRMANCE and proposed **AMICUS CURIAE BRIEF AND ADDENDUM OF NORTH DAKOTA MEDICAL ASSOCIATION IN SUPPORT OF APPELLEES AND IN SUPPORT OF AFFIRMANCE** upon the following by regular United States mail, first class postage prepaid:

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Notary Public

LAURIE A GRIMM
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State of North Dakota
My Commission Expires July 18, 2018

ADDENDUM

OF NORTH DAKOTA MEDICAL ASSOCIATION IN SUPPORT OF APPELLEES AND IN SUPPORT OF AFFIRMANCE

INDEX TO ADDENDUM

ACP

AMERICAN COLLEGE OF PHYSICIANS
INTERNAL MEDICINE | *Doctors for Adults*

STATEMENT OF PRINCIPLES ON THE ROLE OF GOVERNMENTS IN REGULATING THE PATIENT-PHYSICIAN RELATIONSHIP

A Statement of Principles of the
American College of Physicians
July 2012

ADDENDUM 1

Statement of Principles on the Role of Governments in Regulating the Patient-Physician Relationship

A Statement of Principles of the American College of Physicians

This paper, written by Jack Ginsburg and Lois Snyder, JD, was developed for the Health and Public Policy Committee of the American College of Physicians (ACP); Robert M. Centor, MD, FACP, (Chair); Jacqueline W. Fincher, MD, MACP (Vice Chair); Vineet Arora, MD, FACP; Ankit Bhatia (Student); Douglas M. DeLong, MD, FACP; Richard M. Dupee, MD, FACP; Luke O. Hansen, MD; Gregory A. Hood, MD, FACP; Ali M. Khan, MD (Associate); Mary Newman, MD, FACP; Kenneth E. Olive, MD, FACP; P. Preston Reynolds, MD, FACP; Jeffrey G. Wiese, MD, FACP (Regent). The authors wish to thank the members of ACP's Ethics, Professionalism and Human Rights Committee for reviewing and contributing to the development of this paper; David A. Fleming, MD, MA, FACP (Chair); Ana Maria Lopez, MD, MPH, FACP (Vice Chair); Jeffrey T. Berger, MD, FACP; Thomas A. Bledsoe, MD, FACP; Clarence H. Braddock III, MD, MPH, FACP; Nitin S. Damle, MD, MS, FACP; Kathy Faber-Langendoen, MD, FACP; Nathaniel E. Lepp; Alejandro Moreno, MD, MPH, JD, FACP, FCLM; Upasna Swift, MBBS, FACP; Jon C. Tilburt, MD, FACP; Michael N. Young, MD. It was approved by the ACP Board of Regents on July 28, 2012.

Statement of Principles on the Role of Governments in Regulating the Patient-Physician Relationship

American College of Physicians
July 2012

"Society has conferred professional prerogatives on physicians with the expectation that they will use their position for the benefit of patients. In turn, physicians are responsible and accountable to society for their professional actions. Society grants each physician the rights, privileges, and duties pertinent to the patient–physician relationship and has the right to require that physicians be competent and knowledgeable and that they practice with consideration for the patient as a person."
– ACP Ethics Manual (sixth edition, 2012)[1]

Introduction

The physician's first and primary duty is to put the patient first. To accomplish this duty, physicians and the medical profession have been granted a privileged position in society conferred by society and government.[1,2]

Several states have proposed or adopted legislation and/or regulations, however, that interfere, or have the potential to interfere, with appropriate clinical practice by (1) prohibiting physicians from discussing with or asking their patients about risk factors that may affect their health or the health of their families, as recommended by evidence-based guidelines of care; (2) requiring physicians to discuss specific practices that in the physician's best clinical judgment are not individualized to the patient; (3) requiring physicians to provide diagnostic tests or medical interventions that are not supported by evidence or clinical relevance; or (4) limiting information that physicians can disclose to patients. This paper provides a framework for broadly addressing these issues without expressly taking positions on the controversial and related issues of abortion, reproductive rights, and gun control.

Of particular concern are laws and regulations that require physicians to provide care not supported by evidence-based guidelines and/or not individualized to the needs of the specific patient. Although it may be difficult to distinguish between mandates that interfere with clinical practice versus those that promote good public health, this paper attempts to provide a framework with principles that can provide some guidance. The need to address these issues was discussed in April by the Board of Regents, which charged the Health and Public Policy Committee (HPPC), with input from the Ethics, Professionalism and Human Rights Committee (EPHR), to develop a policy framework on laws and regulations that:

1) Prohibit physicians from discussing with or asking their patients about risk factors that may affect their health or the health of their families, as recommended by evidence-based guidelines of care;
2) Require physicians to discuss specific practices if, in the physicians' best clinical judgment, it is not necessary or appropriate at the time of a specific patient encounter; or
3) Require physicians to provide—and patients to receive—diagnostic tests or medical interventions that are not supported by evidence-based guidelines, especially if such tests or interventions are invasive and required to be provided without the patient's expressed consent.

Background

"The physician's first and primary duty is to the patient...[T]he physician's professional role is to make recommendations on the basis of the best available medical evidence and to pursue options that comport with the patient's unique health needs, values, and preferences." In an increasingly complex health care system, physicians have an obligation to help patients understand clinical recommendations to enable them to make informed choices among all appropriate care and referral options.[1]

Government plays a key role in helping to provide the framework within which physicians carry out their ethical obligations. The many appropriate roles of government include licensing, protecting and improving public health, determining the safety and effectiveness of drugs and medical devices, and supporting medical education, training, and research, among others.

The federal government plays a major role in assuring public health, safety, and welfare. Responsibilities include a broad range of functions, such as approving drugs and medical devices for safety and effectiveness, assuring that drugs are manufactured according to proper dosages in safe and uncontaminated facilities, sponsoring clinical health research, supporting the education and training of the physician workforce, assuring a safe environment, and protecting and improving public health. The federal government has a major role in protecting the health and welfare of vulnerable populations, including the elderly (Medicare), the poor and disabled (Medicaid), children (CHIP), veterans (VHA), and other disadvantaged or special needs groups.

All states also have laws and regulations to protect public health, safety, and welfare. State medical practice acts "protect the public from the unprofessional, improper, incompetent, unlawful, fraudulent and/or deceptive practice of medicine." State medical boards regulate the practice of medicine and grant privileges to practice under these laws. The primary responsibility and obligation of the state medical board is to protect the public. They establish requirements for licensure, administer licensure examinations, evaluate the medical education and training of applicants, evaluate previous professional performance of applicants, and establish and administer disciplinary procedures.[3] In doing so, they ensure patients that licensed physicians meet professional standards of care, ethics, and professionalism that, if not met, could compromise patient safety.

These medical practice acts generally defer to the profession to establish and maintain standards of medical and ethical practice. However, medical practice acts can also be quite specific in directing physician behavior. Some state laws require specific actions by physicians and other health care professionals. Examples include laws and regulations requiring immunizations; screening for specific diseases; reporting contagious diseases, suspected cases of child/domestic partner abuse, and reporting of impaired drivers and neglected care of patients in nursing homes and other institutions; rules concerning the treatment of minors; and regulations of hospice care, to name a few. However, legislation can be slow and cumbersome in responding to medical advances or changes in scientific knowledge.

Examples of Legislation and Regulations that Appear to Interfere with Appropriate Clinical Medical Practice and Intrude on the Patient-Physician Relationship

Some recent laws and proposed legislation appear to inappropriately infringe on clinical medical practice and patient-physician relationships, crossing traditional boundaries and intruding into the realm of medical professionalism and could compromise patient safety.

Mandated Treatment and Procedures

Legislation in Alaska[4] would allow patients and families to override a physician's do-not-resuscitate (DNR) order. This legislation fails to recognize the low success rate of cardiopulmonary resuscitation (CPR) and that CPR attempts could be harmful and painful for patients with extremely advanced medical conditions. As stated in the Ethics Manual, "Intervention in the case of a cardiopulmonary arrest is inappropriate for some patients, particularly those for whom death is expected, imminent, and unavoidable." ACP policy allows for unilateral DNR orders by physicians: "In the circumstance that no evidence shows that a specific treatment desired by the patient will provide any medical benefit, the physician is not ethically obliged to provide such treatment (although the physician should be aware of any relevant state law). The physician need not provide an effort at resuscitation that cannot conceivably restore circulation and breathing, but he or she should help the family to understand and accept this reality."[1] And, according to the Charter on Professionalism: "Physicians must have respect for patient autonomy. Physicians must be honest with their patients and empower them to make informed decisions about their treatment. Patients' decisions about their care must be paramount, as long as those decisions are in keeping with ethical practice and do not lead to demands for inappropriate care."[2] The Alaska legislation stipulates that all previously established health care directives and DNR orders become null and void if they are not in accord with the new law.[4]

In Connecticut, Texas, and Virginia, physicians providing mammograms are required to notify women about their breast density and potential benefits of additional screening. In vetoing legislation (SB 791) in California with similar requirements, Gov. Edmund G. Brown Jr. raised concerns about the potential anxiety that such breast density information might provoke. He warned, "The notice contained in this bill goes beyond information about breast density. It advises that additional screening may be beneficial. If the state must mandate a notice about breast density – and I am not certain it should – such a notice must be more carefully crafted, with words that educate more than they prescribe."[5]

Arizona women seeking an abortion must have an ultrasound at least 24 hours before the procedure. Under a recently signed law in Wisconsin, doctors must have three office visits with a woman before prescribing a drug-induced abortion. They also must determine that the woman is not being coerced into the procedure. Physicians who fail to abide by the mandate could be subject to criminal penalties, including imprisonment. In a number of other states, laws also place requirements on abortions.[6]

In Virginia, a bill would have required women to have fetal ultrasound imaging for the purpose of determining gestational age before receiving an abortion.[7] As an external ultrasound would not be able to provide the mandated information early in pregnancy, this legislation would have resulted in the use of transvaginal ultrasound, as determined by her physician, for a woman in the very early stages of pregnancy. In a letter urging Virginia Governor Bob McDonnell to veto the bill, ACP's Virginia Chapter noted, "[W]e believe that this legislation represents a dangerous and unprecedented intrusion by the Commonwealth of Virginia into patient privacy and that it encroaches on the doctor-patient relationship." The letter continued, "[T]his legislation interferes with physicians' ability to make sound clinical judgments based on medical reasoning and in the best interest of our patients."[8] A modified bill, which requires external ultrasound only, was signed into law by Governor Bob McDonnell in March 2012.[9] Any physician who fails to comply is subject to a $2500 civil penalty. Although abortion laws will not be the focus of the position

paper since this procedure is not within the routine practice of internal medicine, we note the issue here because of its prominence in debates about government mandates. It is our goal to develop principles that will be applicable in analyzing a wide variety of laws and regulations.

Prohibited Speech

Laws that restrict the content of patient-physician communications are problematic, especially considering that "[P]hysicians must provide information to the patient about all appropriate care and referral options."[9]

In Florida, legislation expressly restricted health care practitioners from asking patients questions related to gun safety or recording information from those conversations in patients' medical records on penalty of harsh disciplinary sanctions, including fines and permanent revocation of their licenses to practice medicine.[10] Under the law, physicians, following established protocol by informing patients how they may limit the lethal risks posed by firearms, could be at risk of losing their medical licenses. The ACP Florida Chapter joined in an amicus brief arguing that the law would deprive physicians and other health care practitioners of their First Amendment right to freedom of speech, and also would deprive patients of their First Amendment rights to receive potentially life-saving information regarding safety measures they can take to protect their children, families, and others from injury or death resulting from unsafe storage or handling of firearms.[11] The federal district court judge agreed, and a permanent injunction (subject to appeal) has been issued preventing the law from being enforced.[12]

In Pennsylvania, physicians can access information about chemicals used in the "fracking" process to extract oil and natural gas, but they are prohibited by law from discussing their findings with patients who may be suffering from consequent harm. Fracking can involve injecting into the ground toxic chemicals, such as benzene, toluene, ethylbenzene, and xylene.[13] Low levels of exposure to those chemicals can trigger headaches, dizziness, and drowsiness, while higher levels of exposure may cause cancer. The law[14] requires mining and drilling companies to disclose the identity and amount of any chemicals used in fracking fluids upon written request of any health professional seeking the information in order to diagnose or treat a patient that may have been exposed to a hazardous chemical, though health professionals seeking this information must sign a confidentiality agreement stating that they will not disclose the information. However, there is some controversy over whether the law does or does not allow for disclosure to the patient for the purpose of diagnosis and treatment. The following are relevant sections of the statute:

> (10) A vendor, service company, or operator shall identify the specific identity and amount of any chemicals claimed to be a trade secret or confidential proprietary information to any health professional who requests the information in writing if the health professional executes a confidentiality agreement and provides a written statement of need for the information indicating all of the following:
>
> > (i) The information is needed for the purpose of diagnosis or treatment of an individual.
> > (ii) The individual being diagnosed or treated may have been exposed to a hazardous chemical.
> > (iii) Knowledge of information will assist in the diagnosis or treatment of an individual.

(11) If a health professional determines that a medical emergency exists and the specific identity and amount of any chemicals claimed to be a trade secret or confidential proprietary information are necessary for emergency treatment, the vendor, service provider, or operator shall immediately disclose the information to the health professional upon a verbal acknowledgment by the health professional that the information may not be used for purposes other than the health needs asserted and that the health professional shall maintain the information as confidential. The vendor, service provider, or operator may request, and the health professional shall provide upon request, a written statement of need and a confidentiality agreement from the health professional as soon as circumstances permit, in conformance with regulations promulgated under this chapter.[13]

Examples of Other Government Requirements that May be Inappropriate

Laws also govern vaccination of children, with many allowing exemptions for children with medical contraindications confirmed by a physician and exemptions for religious objections or personal beliefs. Concerned that the personal belief exemption is undermining immunization rates, physicians have supported recent bills in Washington state, Vermont, and California to either (1) make the exemption more difficult to obtain by requiring parents to get a physician or nurse practitioner signature affirming they have been provided the parent(s) information on the benefits and risks of immunization and the health risks of communicable diseases covered by the state vaccine mandate, or (2) eliminate the personal belief exemption altogether.[15]

Legislation in New York requires physicians and other health care practitioners, starting in 2011, to offer terminally ill patients "information and counseling regarding palliative care and end-of-life options appropriate to the patient, including...prognosis, risks and benefits of the various options; and the patient's legal rights to comprehensive pain and symptom management." Although the law only requires that the clinician offer to provide information, the Medical Society of the State of New York and others have criticized the law as failing to recognize the complexity and uncertainty involved in end-of-life discussions among a patient, the family, and his or her physician.[16,17] Failure to comply with this law can result in fines of up to $5,000 for repeated offenses, and a jail term of up to 1 year for willful violations. California adopted a similar law in 2009. The California Medical Society did not oppose it, but had opposed an earlier version that would have required doctors to specifically tell terminally ill patients about alternatives, such as palliative sedation and refusing food and water to speed the dying process.[18]

ACP Principles on the Role of Governments and Legislation in Regulating the Patient-Physician Relationship

"Through legislation, administrative action, or judicial decision, government is increasingly involved in medical ethics. The convergence of various forces—scientific advances, patient and public education, the Internet, the civil rights and consumer movements, the effects of law and economics on medicine, and the heterogeneity of our society—demands that physicians clearly articulate the ethical principles that guide their behavior in clinical care, research, and teaching, or as citizens or collectively as members of the profession. It is crucial that a responsible physician perspective be heard as societal decisions are made."
– ACP Ethics Manual (sixth edition, 2012)

The ACP recommends the following principles for the roles of federal and state governments in health care and the patient-physician relationship.

1) All parties involved in the provision of health care, including government, are responsible for acknowledging and lending support to the intimacy and importance of the patient-physician relationship and the ethical obligations of the physician to put the patient first. The fundamental ethical principles of beneficence, honesty, confidentiality, privacy, and advocacy are central to the delivery of evidence-based, individualized care and must be respected by all parties.[1]
2) Physicians should not be prohibited by law or regulation from discussing with or asking their patients about risk factors, or disclosing information (including proprietary information on exposure to potentially dangerous chemicals or biological agents) to the patient, which may affect their health, the health of their families, sexual partners, and others who may be in contact with the patient. Rules limiting what may or may not be discussed, or the information that may be disclosed, during healthcare encounters undermine the patient-physician relationship and can inappropriately affect patient health. The patient and his or her physician are best positioned to determine what topics to discuss.
3) Laws and regulations should not mandate the content of what physicians may or may not say to patients or mandate the provision or withholding of information or care that, in the physician's clinical judgment and based on clinical evidence and the norms of the profession, are not necessary or appropriate for a particular patient at the time of a patient encounter:

    - Even laws and regulations that mandate a test, procedure, treatment, or provision of specific types of health information or counseling to the patient, when generally consistent with the standard of care and intended to provide benefit to the patient, should be approached cautiously, because they cannot allow for all potential situations in which their application would be unnecessary or even harmful to specific patients. Mandated care may also interfere with the patient-physician relationship and divert clinical time from more immediate clinical concerns.
    - Legislation and regulations should not prevent physicians from treating particular types of patients (e.g., based on immigration status, racial or ethnic origin, sexual orientation, religion).[1,19,20]
    - The following questions may be helpful in providing general guidance for evaluating the appropriateness of proposed laws and regulations regarding the provision of medical care during the patient-physician encounter, *with the presumption being that the government should avoid regulating the content of the clinical encounter without a compelling and evidence-based benefit to the individual patient and/or substantial public health justification that can't be better met through other means.* The list is intended merely to suggest questions that should be raised—it is not meant to be all inclusive. The questions are not mutually exclusive; positive answers to all questions does not imply that a law or regulation is appropriate and is not necessary to support a proposed law or regulation.

        a. Is the content and information or care consistent with the best available medical evidence on clinical effectiveness and appropriateness and professional standards of care?

b. Is the proposed law or regulation necessary to achieve public health objectives that directly affect the health of the individual patient, as well as population health, as supported by scientific evidence, and if so, is there any other reasonable way to achieve the same objectives?
c. Could the presumed basis for a governmental role be better addressed through advisory clinical guidelines developed by professional societies?
d. Does the content and information or care allow for flexibility based on individual patient circumstances and on the most appropriate time, setting, and means of delivering such information or care?
e. Is the proposed law or regulation required to achieve a public policy goal –such as protecting public health or encouraging access to needed medical care – without preventing physicians from addressing the healthcare needs of individual patients during specific clinical encounters based on the patients' own circumstances, and with minimal interference to patient-physician relationships?
f. Does the content and information to be provided facilitate shared decision-making between patients and their physicians, based on the best medical evidence, the physician's knowledge and clinical judgment, and patient values (beliefs and preferences), or would it undermine shared decision-making by specifying content that is forced upon patients and physicians without regard to the best medical evidence, the physician's clinical judgment and the patient's wishes?
g. Is there a process for appeal to accommodate for specific circumstances or changes in medical standards of care?

4) In making decisions about counseling and treatment among evidence-based options, the patient's values are paramount, although the physician is not required to violate standards of medical care or ethics, fundamental personal values, or the law. Patients should not be required to undergo tests or interventions, especially invasive and potentially harmful interventions, that violate the patient's values, are not medically necessary, and are not supported by scientific evidence on clinical effectiveness or could expose the patient to unnecessary risk, and physicians should not be required to provide such services.

5) Medical practice should reflect current scientific evidence and medical knowledge, which may evolve over time. Physicians should be guided by evidence-based clinical guidelines that allow flexibility to adapt to individual patient circumstances. Statutory and regulatory standards of care may become "set in concrete" and not reflect the latest evidence and applicable medical knowledge.

6) Laws governing medical practice must be revised as needed and regulatory rules should offer a process for timely appeal in an interval appropriate to the nature of the condition being treated.

7) Regulatory requirements should not create undue burdens that have the consequence of limiting access to needed care or unnecessarily divert from the precious time that physicians have to spend with patients.

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Product #

ADDENDUM 12

GOV2001

ASHP Statement on the Use of Medications for Unlabeled Uses

The freedom and responsibility to make drug therapy decisions that are consistent with patient-care needs is a fundamental precept supported by ASHP. This activity is a professional duty of pharmacists not limited by language in Food and Drug Administration (FDA)-approved product labeling.

The prescribing, dispensing, and administration of FDA-approved drugs for uses, treatment regimens, or patient populations that are not reflected in FDA-approved product labeling often represent a therapeutic approach that has been extensively studied and reported in medical literature. Such uses are *not* indicative of inappropriate usage. Health-care professionals should appreciate the critical need for freedom in making drug therapy decisions and understand the implications of unlabeled uses. ASHP supports third-party reimbursement for FDA-approved drug products appropriately prescribed for unlabeled uses.

Definition of Unlabeled Use

The FDA approves drug products for marketing in the United States. Such a product approved for marketing is often termed an "FDA-approved drug." FDA also approves each drug product's labeling (container label, package insert, and certain advertising); the term "FDA-approved labeling" applies here. Drug uses that are not included in the indications or dosage regimens listed in the FDA-approved labeling are defined as "unlabeled uses." For purposes of this document, unlabeled use includes the use of a drug product in (1) doses, (2) patient populations, (3) indications, or (4) routes of administration that are not reflected in FDA-approved product labeling.

It is important to recognize that FDA cannot approve or disapprove physician prescribing practices of legally marketed drugs. FDA does regulate what manufacturers may recommend about uses in their products' labeling and what manufacturers can include in advertising and promotion.

The sometimes-used term "unapproved use" is a misnomer, implying that FDA regulates prescribing and dispensing activities. This term should be avoided.[1] Other terminology that is sometimes used to describe unlabeled use includes "off-label use," "out-of-label use," and "usage outside of labeling."

According to FDA, unlabeled use encompasses a range of situations that extend from inadequate to carefully conceived investigations, from hazardous to salutary uses, and from infrequent to widespread medical practice. Accepted medical practice often involves drug use that is not reflected in FDA-approved drug-product labeling.[2]

Health-Care Issues Related to Unlabeled Use

Access to Drug Therapies. The prescribing and dispensing of drugs for unlabeled uses are increasing.[3,4] In many clinical situations, unlabeled use represents the most appropriate therapy for patients. Failure to recognize this or, more importantly, regarding such use as "unapproved" or "experimental" may restrict access to necessary drug therapies.

Lack of Practice Standards. Well-defined medical practice standards that differentiate between experimental therapies and established practice will probably always be somewhat lacking, owing to the advancement of medical science and the dynamic nature of medical practice. Standards of practice for certain drug therapies, particularly biotechnologically produced drugs, cancer chemotherapy, and AIDS treatments, are continually evolving. The dynamic nature of these drug therapies makes it difficult for professional societies to review scientific data expediently and to develop standards that remain absolutely current.

Failure of Package Insert and FDA-Approved Labeling to Reflect Current Practice. For FDA-approved product labeling to be modified, scientific data must be submitted by a product's manufacturer to FDA to support any additional indication(s) and dosage regimen(s). Once they are submitted, FDA must review the data and make a decision to permit alteration of the package insert.

Knowing that unlabeled uses are permitted, and knowing that the accumulation and submission of scientific data to FDA to modify labeling is a time-consuming and often expensive process, some pharmaceutical manufacturers elect not to pursue labeling changes. Therefore, a product's labeling sometimes fails to represent the most current therapeutic information for a drug, and situations naturally occur when it is appropriate to prescribe drugs for unlabeled uses.

Pharmacist's Role

ASHP believes that pharmacists in organized health-care settings bear a significant responsibility for ensuring optimal outcomes from all drug therapy. With respect to unlabeled uses, the role of the pharmacist should be to

1. Fulfill the roles of patient advocate and drug information specialist.
2. Develop policies and procedures for evaluating drug orders (prescriptions) and dispensing drugs for unlabeled uses in their own work settings. Such policies and procedures might address the documentation of scientific support, adherence to accepted medical practice standards, or a description of medical necessity.
3. Develop proactive approaches to promote informed decisionmaking by third-party payers for health-care services.

Role of Drug Information Compendia

The Medicare Catastrophic Coverage Act of 1988 (now repealed) included the statements that "in carrying out the legislation, the Secretary [of Health and Human Services] shall establish standards for drug coverage. In establishing such standards, which are based on accepted medical practice, the Secretary shall incorporate standards from such current authoritative compendia as the Secretary may select."[5] Specific compendia recommended were the *AHFS Drug Information*,

AMA Drug Evaluations, and *USP Dispensing Information, Volume I*. Despite the repeal of the Act, some third-party payers have adopted guidelines that endorse these three compendia as authoritative information sources with respect to unlabeled uses for drug products.

Positions on Unlabeled Use

FDA Position. A statement entitled "Use of Approved Drugs for Unlabeled Indications" was published in the *FDA Drug Bulletin* in April 1982 to address the issues of appropriateness and legality of prescribing approved drugs for uses not included in FDA's approved labeling. This statement included the following:

> *The Food, Drug and Cosmetic Act does not limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.*[1]

Other Organizations. Other organizations that have published positions on the issue of unlabeled uses of drug products are the Health Care Financing Administration (HCFA),[6] the Blue Cross and Blue Shield Association of America (BC/BS),[7] and the Health Insurance Association of America (HIAA).[8]

The American Medical Association, American Society of Clinical Oncology, Association of American Cancer Institutes, Association of Community Cancer Centers, Candlelighters Childhood Cancer Foundation, Memorial Sloan Kettering Cancer Center, National Cancer Institute, and the National Institute of Allergy and Infectious Diseases jointly developed a consensus statement and recommendations regarding use and reimbursement of unlabeled uses of drug products.[9]

These statements are consistent with the ASHP position.

Reimbursement Issues

As a cost-containment measure, most third-party payers exclude coverage for experimental therapies. Drug therapy coverage decisions are complicated, because often it is difficult to differentiate among an accepted standard of practice, an evolving standard of practice, and investigational therapies. Data demonstrating medical necessity and improved patient outcome are often difficult to retrieve. Consequently, insurance carriers and managed care providers have sometimes elected to cover only those indications included in FDA-approved drug-product labeling and have frequently denied coverage for unlabeled uses of drug products.

ASHP believes that such coverage denials restrict patients from receiving medically necessary therapies that represent the best available treatment options. A growing number of insurance carriers are following the BC/BS and HIAA guidelines that encourage the use of the three authoritative drug compendia, peer-reviewed literature, and consultation with experts in research and clinical practice to make specific coverage decisions. ASHP supports informed decisionmaking that promotes third-party reimbursement for FDA-approved drug products appropriately prescribed for unlabeled uses.

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Lysol-Induced Criminal Abortion

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THE METHODS AND DRUGS used in performing criminal abortions are legion. Recently several patients with criminal abortions induced by Lysol,* one of the more rare abortifacients, were admitted to this hospital. Lysol had been given as an intrauterine douche to 4 gravid women. Toxication was severe enough to cause one death.

The diagnosis of criminal abortion is difficult, for symptoms and complications are variable and the patient is often reluctant to give a complete history.

Because of the unusual nature of these cases it seems warranted to record brief abstracts together with a partial review of the literature.

CASE REPORT

Case 1

M. B., age 32, was in a hysterical state when admitted to the emergency room. She denied any amenorrhea but said she had given herself a "hot douche." The only other history available at admission was obtained from her husband, who said she had complained of abnormal vaginal bleeding. Later the patient admitted having had pain in her thighs and generalized aching.

Examination revealed a temperature of 104° F., blood pressure 112/70, pulse 100, and bloody sputum. The cervix was closed and the uterus was slightly enlarged and nontender. The urine was port-wine color and contained 4+ albumin. Because of extensive hemolysis in the blood sample, hematologic studies were inaccurate but were reported as follows: hemoglobin 7.5 Gm., white blood count 35,000, and nonprotein nitrogen 58.5.

Further inquiry disclosed that the patient had been under the care of a physician who had treated her the previous week for a threatened abortion. The patient and her husband then admitted that 2 days prior to admission this physician had introduced Lysol by catheter into the uterus to induce abortion.

Four hours after admission, the patient became extremely restless and it was necessary to utilize sedation and restraints. Thereafter she complained of lower abdominal cramps and slight vaginal bleeding. Supportive therapy, including intravenous fluids and antibiotics, was employed. Attempts to type and cross-match the patient's blood were unsuccessful because of extensive hemolysis; however, she was given 500 cc. of Group O Rh-negative whole blood.

Response was unsatisfactory. In less than 2 hours, hyperpnea appeared and the patient became comatose. Oxygen therapy was begun because of moist rales throughout both lungs. Her pulmonary edema progressed and she died approximately 12 hours after admission.

Autopsy disclosed massive hemolysis with resultant discoloration of all tissues, most pronounced in the liver and kidneys. Focal necrosis of the liver was noted. The kidneys showed an acute hemoglobinuric nephrosis. The uterus was slightly enlarged and contained well-preserved placental tissue. Severe pulmonary edema, hydrothorax, and many areas of oil emboli were present.

Phenol group determinations on the liver and placenta were strongly positive.

Death was believed to have been caused by massive hemolysis, pulmonary oil embolism, and phenol poisoning.

Case 2

M. E., age 28, came to the hospital when slight vaginal bleeding of approximately one month's duration became profuse. After considerable questioning, she stated that 2 days after the onset of bleeding a "substance" had

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* Lysol is a mixture of 50 per cent saponified linseed oil and cresol, a member of the phenol group.

been injected into her "womb" by her physician. It was later established that she and the patient in Case 1 had been attended by the same physician.

Examination revealed a temperature of 100° F., blood pressure 90/70, pulse 120. The uterus was enlarged and the cervix was soft, bluish, and partially dilated. Hematologic studies reported a hemoglobin of 7 Gm.; hematocrit, 27 per cent, and no hemolysis.

The patient was given antibiotic therapy and whole-blood transfusions. Curettage removed a moderate amount of slightly necrotic tissue. The odor of phenol was noticeable in this tissue. The patient's temperature was 100.8° F. postoperatively and remained slightly elevated for 2 days. Her subsequent recovery was uneventful.

The pathology report was: necrotic products of conception; the tissue contained phenol compounds.

Case 3

M. K., age 35, was admitted because of vaginal bleeding of 2 weeks' duration. She said that 1 week prior to admission, her physician had given her a prescription for medicine, but she denied having been criminally aborted. Further information established this physician as the one who had attended the two previous patients.

On examination her temperature was 99.6° F., blood pressure 100/60, pulse 120. The uterus was enlarged to that of a 2-months gestation, the cervix was dilated, and there was slight vaginal bleeding. Hemoglobin was reported as 3.33 Gm., the hematocrit as 11 per cent, and the white blood count as 14,250.

The patient's response to antibiotic therapy and whole-blood transfusions was unsatisfactory. Approximately six hours after admission her temperature rose to 103° F. A pelvic examination disclosed a foul vaginal discharge which had an odor typical of phenol. A second blood sample showed moderate hemolysis with an estimated hemoglobin of 2.25 Gm., and a hematocrit of 12 per cent. The urine contained no hemoglobin or albumin.

A necrotic placenta was removed by curettage and a uterine pack was inserted because of abnormal bleeding. After surgery the patient's temperature was 97.0° F. and continued to be subnormal for several days. Her recovery was otherwise uneventful.

The pathology report was: necrotic products of conception; the tissue contained phenol compounds.

Case 4

G. M., age 18, came because of vaginal bleeding and lower abdominal cramps after a loss of water through the vagina. She gave a history of amenorrhea of 4 months' duration.

On examination her temperature was 102° F., blood pressure 100/70, and pulse 90. The uterus was enlarged to that of a 4-months gestation, the cervix was dilated, and no fetal heart tones were heard. The characteristic odor of phenol was noted in the vagina. Her hemoglobin was 11.11 Gm., the hematocrit 34 per cent, and the white blood count 24,000.

Shortly after admission the patient spontaneously aborted a macerated fetus, estimated to be of 20 weeks' gestation. The placenta was delivered intact. The patient continued to have abdominal discomfort 1 week postabortal and had a mild parametritis.

Phenol was demonstrated in the fetal and placental tissues.

DISCUSSION

Phenol is a toxic protoplasmic poison and produces coagulation of tissues in a dilution of 1:1000. When taken orally in a lethal dosage of 10 to 12 Gm., phenol causes depression, weakness, nausea, vomiting, abdominal pain, respiratory failure, and vertigo;[4, 5, 6, 8, 9, 11] coma ensues and death follows. Cresol, a component of Lysol, has a similar toxicity.[4]

In a partial review of the literature only one report was found on the use of Lysol or other phenol compounds as abortifacients. Vance reported a case in which the patient died of pulmonary oil embolism. The necropsy observations were similar to those given in the fatal case of this report.

The chemical identification of phenol and related compounds in the tissue in the 4 cases reported here was made by the diazoaniline coupling reaction test.* Since small amounts of phenol-like compounds are present in normal tissue,[3] control samples of normal placenta were assayed concurrently with placental tissues of the 4 patients. The control tests were negative to faintly positive and were easily differentiated from the

* Tests were made in the laboratory of the State Medical Examiner.

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strongly positive reactions on the study tissue.

In contrast to the paucity of material on intrauterine phenol injection, many publications reported the use of various intrauterine pastes for inducing therapeutic and criminal abortions.[1, 2, 10, 12, 11]

Intrauterine pastes were first utilized for therapeutic abortion by Leunbach in 1928. This practice was extensively employed in Europe and was introduced into the United States in 1930. Most of the pastes had a soft soap as the basic ingredient. Dutra, Cleveland, and Lyle found this soap to be the lethal agent in these abortifacients.

Shortly after the introduction of the soft soap pastes, reports of deaths following their use appeared in the literature.[2, 7, 10, 12, 14] Weilerstein, reporting on several patients who had been aborted, summarized the effects of the paste as follows: (1) Blood destruction and hemolysis produce jaundice in the mild cases and death when the viscera are significantly involved. (2) Pulmonary embolism is common and is fatal when massive. (3) Infections occur in the pelvis, with spreading peritonitis, celitis, and septicemia in the more severe cases. (4) Local tissue necrosis is frequent, often precipitating profuse hemorrhage.

Animal experimentation by D'Amour and Kiven verified the dangers of the intrauterine pastes. One of these abortifacients was injected into the pregnant uteri of 44 rats. All of the animals aborted and none were able to conceive again. Fourteen per cent of the animals died because of a generalized infection of the abdominal cavity.

SUMMARY

Four cases of Lysol poisoning from criminal abortion have been reported together with a partial review of the literature. In these patients the clinical picture was similar to that reported for Lysol poisoning generally and may be summarized as follows:

1. All the abortions were incomplete. The fetal tissue showed unusual preservation and contained phenol compounds.

2. Lysol toxication was manifested by central nervous system irritability, shock, tachycardia, leukocytosis, hemolysis, and fever.

3. Respiratory embarrassment was noted and was associated with pulmonary edema and/or oil emboli.

4. Local tissue necrosis may have exaggerated the uterine hemorrhage.

5. There was moderate to severe anemia from both hemorrhage and hemolysis.

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ADDENDUM 17

REVIEW ARTICLE

CURRENT CONCEPTS

SEPTIC ABORTION

PHILLIP G. STUBBLEFIELD, M.D., AND DAVID A. GRIMES, M.D.

SEPTIC abortion, an abortion associated with infection and complicated by fever, endometritis, and parametritis,[1] remains one of the most serious threats to the health of women throughout the world. Morbidity and mortality from septic abortion are infrequent in countries where induced abortion is legal but are widespread in the many developing countries where it is either illegal or inaccessible. Septic abortion provides a paradigm for preventive medicine, with opportunities for primary, secondary, and tertiary prevention.[2]

SCOPE OF THE PROBLEM

A 1973 report described an adolescent admitted to a large Boston teaching hospital with what proved to be incomplete septic abortion. Uterine evacuation was not performed until several days after admission, because the diagnosis of incomplete septic abortion had not been considered initially. The patient died despite treatment with massive doses of antibiotics and intensive medical management.[3] Tragedies of this sort are now rare.

The most important effect of the legalization of abortion on public health in the United States[3] was the near elimination of deaths from illegal abortion. Deaths from illegal abortion are mainly due to infection.[4,5] A 1990 review of deaths due to abortion in the United States noted that 62 percent of deaths from illegal abortion and 51 percent of deaths from spontaneous abortion were due to infection, as compared with only 21 percent of deaths from legal abortion.[6] The risk of death from postabortion sepsis is highest for young women, those who are unmarried, and those who undergo procedures that do not directly evacuate the contents of the uterus.[7] With more advanced gestation, there is a higher risk of uterine perforation and retained tissue.[7] A delay in treatment allows the infection to progress to bacteremia, pelvic abscess, septic pelvic thrombophlebitis, disseminated intravascular coagulopathy, septic shock, renal failure, and death.[8]

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Maternal mortality from all causes has declined rapidly in the United States since 1940.[9] Changes in maternal mortality related to abortion have occurred in three phases: a decline in mortality from 1940 until 1950, a plateau from 1951 to 1965, and a rapid decline — more rapid than that of maternal mortality from other causes — from 1965 to 1976, as legal abortion became increasingly available. In 1987, the last year for which complete data are available, there were 1,353,671 legal, induced abortions, 6 of which resulted in death, for a case fatality rate of 0.4 per 100,000 legal abortions.[6] In comparison, over 1000 women per year died from abortion in the 1940s.[5] The American Medical Association's Council on Scientific Affairs has attributed the marked decline in deaths related to abortion during this century to the introduction of antibiotics to treat sepsis; the widespread use of effective contraception beginning in the 1960s, which reduced the number of unwanted pregnancies; and more recently, the shift from illegal to legal abortion.[10] Serious complications have become rare as well.[11]

The experience in Western Europe has been very similar to that in the United States, with very low rates of abortion-related mortality once legal abortion became widely available.[12] Overall, mortality from legal abortion in Europe is less than 1 death per 100,000 procedures. The rate is somewhat higher in the former Soviet Union, where illegal abortion, with a markedly higher risk of death, has emerged as a problem.[13]

Abortion remains a primary cause of maternal death in Third World countries. The World Health Organization estimates that 25 to 50 percent of the 500,000 maternal deaths that occur every year result from illegal abortion.[14] Most of these deaths occur in underdeveloped countries. The data on preventable morbidity and mortality from septic abortion are staggering and well documented.[15-23] Abortion-related deaths result primarily from sepsis.[20,21] The problem may actually be escalating in some areas. In Rio de Janeiro, Brazil, for example, maternal mortality increased almost fourfold from 1978 to 1987 (from 128 to 462 deaths per 100,000 live births); abortion-related deaths accounted for 47 percent of the total maternal mortality.[22]

PRIMARY PREVENTION OF SEPTIC ABORTION

Primary prevention is defined as an intervention made to avert disease or injury.[2] Primary prevention of septic abortion includes provision of effective and acceptable contraception; provision of safe, legal abortion services in the case of contraceptive failure; and appropriate medical management of abortion.

Pregnancy places a woman at some risk for illness and death. This risk may be gladly assumed with a desired pregnancy. Unwanted pregnancy places a

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woman at additional risk if she seeks abortion and safe services are not available.[23,24] A reduction in the number of unwanted pregnancies is a goal that both sides in the abortion controversy can agree on, though the proposed means to that end diverge.

A prerequisite to preventing unwanted pregnancy is sexual equality, so that women can avoid coercive sexual relationships and use contraceptive methods that they regard as safe and free of side effects.[24] In the United States, age-specific abortion ratios make it clear that the women at highest risk for unwanted pregnancy are adolescents and young adults.[25]

The need for safe, legal abortion is clearly shown by the Romanian experience. When abortion was outlawed in the 1960s, the rate of abortion-related mortality rose 10-fold. Over 23 years, an estimated 10,000 women died because of the imposition of this policy.[26] The death rate fell only when abortion was once again legalized.

The risk of death from abortion rises from the first trimester of pregnancy to the second.[5] Therefore, safe services are needed early in pregnancy. Access to such services is a problem, especially for adolescents, who in many jurisdictions must obtain consent from their parents for an abortion and may instead continue the pregnancy — a far more dangerous course — on their own.[27]

The procedure for an abortion early in the pregnancy is not complicated (Table 1). In the first trimester and early second trimester, abortion is readily performed by vacuum curettage in an outpatient clinic or office.[28,29] Prophylactic antibiotics reduce the risk of fever after abortion.[30-32]

Table 1. Procedure for Performing a Safe Abortion in the First Trimester of Pregnancy.*

Confirm the pregnancy with a urine pregnancy test.
Provide nonjudgmental counseling.
Evaluate the patient for any active illness that may complicate the procedure or choice of anesthetic and for allergies.
Perform a physical examination.
Perform a pelvic examination with attention to the size and position of the uterus and other signs of pelvic pathology.
Obtain an ultrasound examination if the period of gestation is uncertain, there is a discrepancy between the duration of amenorrhea and the size of the uterus, there is a pelvic mass, or the pregnancy has progressed beyond early midtrimester.
Determine blood type and Rh at a minimum; hematocrit, screening tests for gonorrhea, chlamydia, human immunodeficiency virus, and syphilis, as well as cervical cytologic studies, are optional but recommended.
Administer prophylactic antibiotics (oral doxycycline, two doses of 100 mg each).
Encourage the patient to choose local anesthesia (paracervical block).
Dilate the cervix with tapered dilators (Pratt or similar type) or use hygroscopic dilators (laminaria or a synthetic alternative).†
Use a vacuum cannula with a diameter appropriate for the size of the uterus (1 mm smaller than the estimated gestational age in weeks).
Examine tissue to rule out incomplete or failed abortion and ectopic or molar pregnancy.
Provide access to 24-hour follow-up services.
Closely monitor patients at high risk for incomplete abortion or ectopic pregnancy.

*Summarized from Herr[28] and Stubblefield.[29]
†Dilapan (Gynetech, Lebanon, N.J.) or Lamicel (Cabot Laboratories, Langhorne, Pa.).

Secondary Prevention of Septic Abortion

Secondary prevention is defined as early detection and treatment with the goal of halting the disease process.[2] Secondary prevention of septic abortion entails prompt diagnosis and effective treatment of endometritis to avert more serious infections. The diagnosis of septic abortion must be considered when any woman of reproductive age presents with vaginal bleeding, lower abdominal pain, and fever. A common feature in reported cases of death from septic abortion is delayed treatment: a young or unmarried woman, reluctant to reveal that she has had an abortion, delays seeking help until she is moribund. In these circumstances, a sensitive pregnancy test (capable of detecting 20 to 50 mIU of the beta subunit of human chorionic gonadotropin per milliliter) is usually positive, since it takes four to six weeks for β-human chorionic gonadotropin to become undetectable after complete uterine evacuation.

A rapid initial assessment is needed to determine the severity of the problem. If the patient has had symptoms for several days, a generalized, serious illness may be present. When possible, the person who performed the abortion should be contacted to determine the details of the procedure, the results of any bacteriologic studies, and the results of pathological examination of aborted tissue. Illegal abortion performed by insertion of rigid foreign objects increases the risk of perforation,[33] and intrauterine instillation of soap solutions containing cresol and phenol poses the risk of uterine necrosis, renal failure, toxicity to the central nervous system, cardiac depression, and respiratory arrest.[34]

The abdominal and pelvic examinations are of great importance. The examiner should note abdominal tenderness, guarding, and rebound and determine whether tenderness is limited to the lower abdomen (pelvic peritonitis) or is present throughout the abdomen (generalized peritonitis). Are vaginal or cervical lacerations present? Is there a foul odor or pus or are the products of conception visible in the cervical os? Is the uterus enlarged and tender? Is there an adnexal mass? If there is a suspicion of perforation, radiographic studies of the abdomen may help identify free air or foreign bodies. Disseminated sepsis is suggested by high fever and prostration, tachycardia, tachypnea, respiratory difficulty, and low blood pressure.[8,35]

Some women have a mild illness characterized by the triad of low-grade fever, mild lower abdominal pain, and moderate vaginal bleeding. Patients presenting with these symptoms usually have either incomplete or failed abortion (continuing pregnancy) or hematometra (retained clotted and liquid blood).[36] Ideal management is immediate re-evacuation in the ambulatory clinic or the emergency room. This can be accomplished safely and humanely by vacuum curet-

tage with local anesthesia and intravenous sedation. In a large U.S. series, 3.5 patients per 1000 underwent re-evacuation in the abortion clinic, which undoubtedly contributed to the remarkably low rate of hospitalization for septic abortion (0.21 per 1000 abortions).[11]

The bacteria associated with septic abortion are usually polymicrobial, derived from the normal flora of the vagina and endocervix, with the important addition of sexually transmitted pathogens.[37] Gram-positive and gram-negative acrobes and facultative or obligate anacrobes, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* are all possible pathogens.[8] In the United States, infection with *Clostridium perfringens* is largely associated with illegal abortion.[8,35] In Third World countries, tetanus is a cause of mortality from septic abortion.[15] Because of the variety of bacterial agents that can be associated with septic abortion, no one antibiotic agent is ideal. The regimens recommended for outpatient management of pelvic inflammatory disease are appropriate for early postabortion infection limited to the uterine cavity. One such regimen is ofloxacin plus either clindamycin or metronidazole.[38] Evaluation of the patient 48 hours after the start of treatment is essential, with hospitalization if fever and pain persist.

Tertiary Prevention of Septic Abortion

Tertiary prevention is intervention to minimize the harm done by a disease and reduce the disability it produces.[2] In the case of septic abortion, the purpose of tertiary prevention is to avert the serious consequences of infection, including conditions requiring a hysterectomy and death. Patients with established infection, as indicated by a high temperature (arbitrarily defined as >38°C), pelvic peritonitis, or tachycardia, should be hospitalized for parenteral antibiotic therapy and prompt uterine evacuation. Bacteremia, which is more common with septic abortion than with other pelvic infections, may result in septic shock and the adult respiratory distress syndrome.[35] Management of severe sepsis requires eradication of the infection and supportive care for the cardiovascular system and other involved organ systems.[8,36,39]

Eradicating the Infection

Blood, urine, and cervical specimens should be cultured, and high doses of broad-spectrum antibiotics begun intravenously. Tissue obtained during an endometrial biopsy or uterine aspiration provides a better specimen for culture than does cervical discharge. Examination of the Gram-stained material can guide early management.

A time-honored regimen for severe pelvic sepsis is penicillin (5 million units given intravenously every six hours) or ampicillin (2 to 3 g given intravenously every six hours) combined with clindamycin (900 mg given intravenously every eight hours) and an aminoglycoside, either gentamicin or tobramycin (a loading dose of 2 mg per kilogram of body weight, followed by 1.5 mg per kilogram every eight hours, depending on the blood level and renal status).

Emptying the Uterus

Any tissue remaining from the pregnancy must be evacuated without delay as soon as antibiotic therapy and fluid resuscitation have been started. Hesitating to evacuate the uterus because of the poor condition of the patient is a common mistake in the management of septic abortion that proves fatal.[7] Vacuum curettage is readily accomplished under local anesthesia with minimal intravenous sedation and, if necessary, can be performed in an intensive care unit.

A retained fetus from a midtrimester abortion poses a special challenge. An experienced practitioner can usually evacuate the uterus successfully with curettage guided by ultrasonography. If an experienced practitioner is not readily available, a medical means for uterine evacuation is needed. The use of prostaglandin E_2, or dinoprostone (20-mg vaginal suppositories), is contraindicated in patients with sepsis because it elevates the body temperature. A better alternative is the 15-methyl analogue of prostaglandin $F_{2\alpha}$, carboprost tromethamine, given as an intramuscular injection of 250 μg every two to three hours. It is contraindicated in patients with asthma.

Alternatively, high doses of oxytocin can be used. A dose of 50 units of oxytocin given in 500 ml of 5 percent dextrose and normal saline over a three-hour period is followed by a one-hour rest and then repeated, with an additional 50 units of oxytocin in the next 500-ml infusion. This regimen is repeated, with an additional 50 units of oxytocin with each infusion, until the fetus aborts or a dose of 300 units of oxytocin in 500 ml is reached.[40]

If none of these means is available, a metreurynter can be used. A Foley catheter with a 50-ml balloon attached is placed in the lower uterus. One kilogram of traction from an orthopedic weight at the foot of the bed is then applied to the catheter, which dilates the cervix and stimulates contractions.

The Role of Laparotomy

Laparotomy will be needed if there is no response to uterine evacuation and adequate medical therapy. Other indications for laparotomy are uterine perforation with a suspected bowel injury, a pelvic abscess, and clostridial myometritis.[35] Although ultrasonographically guided percutaneous needle aspiration of a pelvic abscess is sometimes used, the technique is still new, and in critically ill women with severe postabortion sepsis, a hysterectomy will probably be needed in addition to drainage of the abscess. A discolored, woody appearance of the uterus and adnexa, suspected clostridial sepsis, crepitation of the pelvic tissue, and radiographic evidence of air within the uterine wall are indications for a total hysterectomy and re-

moval of both uterine adnexae. Tissue specimens for culture should be obtained during surgery. Copious irrigation of purulent material and drainage of the peritoneal cavity with a closed suction system are advised. The fecal stream should be diverted by an enterostomy if there is a bowel injury.

The abdomen should be closed with interrupted internal stays (Smead–Jones or similar stays) or a running mass ligature of the peritoneum, rectus muscles, and rectus fascia. The subcutaneous layer and skin are left open, with sutures placed for a delayed primary closure, and the wound is packed.

Supportive Care

Severe sepsis and septic shock should be managed in an intensive care setting in collaboration with physicians and nurses trained in critical care medicine. Cardiovascular support is provided in an attempt to restore close-to-normal blood pressure and tissue perfusion.[35,41,42] Other than the need to ensure evacuation of the uterus, the principles of management of postabortion septic shock do not differ from those of septic shock from other causes. An arterial line, a balloon-flotation right-heart catheter, and an indwelling urinary catheter are inserted. Fluid resuscitation is used to maximize ventricular performance by achieving a target value for the mean arterial pressure without exceeding a target value for the pulmonary-capillary wedge pressure. Vasopressors, dopamine, and dobutamine are added if the pulmonary-capillary wedge pressure becomes elevated before the target mean arterial pressure is reached.

The adult respiratory distress syndrome develops in 25 to 50 percent of patients with septic shock.[39] Tissue oxygenation should be monitored with blood gas measurements and pulse oximetry, and mechanical ventilation begun early if the oxygen saturation falls below 90 percent or if the pulmonary compliance begins to decrease.

Since two randomized trials failed to find a benefit in high-dose corticosteroid therapy, it is no longer recommended.[43,44] A human monoclonal antibody that binds endotoxin is available in Europe,[45] and a monoclonal antibody to tumor necrosis factor has been reported to be beneficial.[46] These agents are very expensive, however, and their clinical role remains to be established. Hyperbaric oxygenation in combination with effective surgical and antibiotic therapy may improve the outcome in women with clostridial myonecrosis.[47]

Conclusions

Serious complications and death from abortion-related infection are almost entirely avoidable. Unfortunately, the prevention of death from abortion remains more a political than a medical problem. Although leaders in international health have repeatedly drawn attention to postabortion complications and mortality, many governments and health care agencies still lack the moral courage to confront the problem.[14,48] For health care professionals, the ethical obligation has been clearly defined: we have a duty "to affirm our own commitment to health values. We are obligated to put health first, to do so by respecting the best scientific evidence, and to be frank when we put aside such evidence for other considerations, be they moral, or religious, or economic, or simply expedient."[49]

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TIMOTHY HOLTZ, M.D.

ADDENDUM 22

Resolution No. 4

Introduced By: **NDMA Commission on Legislation**

Subject: **Protecting The Patient-Physician Relationship**

1) **WHEREAS,** The protection of the sanctity of the patient-physician relationship, including defending the freedom of communication between patients and their physicians, is a core priority of NDMA; and

2) **WHEREAS,** The health and well-being of patients depends upon a collaborative effort between physician and patient; and

3) **WHEREAS,** Physicians must have the ability to freely communicate with their patients and provide information to patients about their health and safety, without fear of intrusion by government or other third parties; and

4) **WHEREAS,** Legislation which interferes with the patient-physician relationship can not only infringe on physicians' First Amendment right to freedom of speech, but also potentially can put physicians in an untenable position of risking disciplinary proceedings or criminal prosecution, and could interfere with patient safety and with the patient's ability to have access to adequate medical information;

THEREFORE, BE IT RESOLVED BY THE 2012 HOUSE OF DELEGATES OF THE NORTH DAKOTA MEDICAL ASSOCIATION that that the North Dakota Medical Association adopt the following principles and,

BE IT FURTHER RESOLVED, that NDMA communicate these principles to the North Dakota State Legislature.

It is the policy of the NDMA to oppose interference by the government and third parties that causes a physician to compromise his or her medical judgment as to what information or treatment is in the best interest of the patient.

NDMA will work with other organizations to oppose legislation or state or federal rules or regulations that interfere with the patient-physician relationship or that prevent physicians from freely discussing with, or providing information to, patients about medical care and procedures, or which direct physicians to provide specified information or perform specified tests that are not medically necessary. NDMA will communicate to government entities and to the public the concerns inherent in rules, regulations or statutes that restrict or direct communication between physicians and their patients as stated in this policy.

Adopted October 22, 2012
Fadel Nammour, MD
Speaker of the House

ADDENDUM 23

SOUNDING BOARD

Legislative Interference with the Patient–Physician Relationship

Steven E. Weinberger, M.D., Hal C. Lawrence III, M.D., Douglas E. Henley, M.D., Errol R. Alden, M.D., and David B. Hoyt, M.D.

Increasingly in recent years, legislators in the United States have been overstepping the proper limits of their role in the health care of Americans to dictate the nature and content of patients' interactions with their physicians. Some recent laws and proposed legislation inappropriately infringe on clinical practice and patient–physician relationships, crossing traditional boundaries and intruding into the realm of medical professionalism. We, the executive staff leadership of five professional societies that represent the majority of U.S. physicians providing clinical care — the American Academy of Family Physicians, the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, the American College of Physicians, and the American College of Surgeons — find this trend alarming and believe that legislators should abide by principles that put patients' best interests first. Critical to achieving this goal is respect for the importance of scientific evidence, patient autonomy, and the patient–physician relationship.

Examples of inappropriate legislative interference with this relationship are proliferating, as lawmakers increasingly intrude into the realm of medical practice, often to satisfy political agendas without regard to established, evidence-based guidelines for care. Of particular concern are four specific types of laws or legislative proposals.

The first type of law prohibits physicians from discussing with or asking their patients about risk factors that may affect their health or the health of their families, as recommended by evidence-based guidelines of care. In 2011, for example, Florida enacted the Firearm Owners' Privacy Act, which substantially impaired physicians' ability to deliver gun-safety messages to patients.[1] The law also prohibited practitioners from routinely inquiring about whether patients own firearms and recording this information in a patient's medical record. Practitioners who violated the law were potentially subject to severe disciplinary action, including fines and loss of licensure. The concerns we have about this law were well explained by U.S. District Judge Marcia G. Cooke, who issued a permanent injunction on June 29, 2012, barring the law's enforcement. As Cooke noted in the opinion, "The State, through this law, inserts itself in the doctor–patient relationship, prohibiting and burdening speech necessary to the proper practice of preventive medicine, thereby preventing patients from receiving truthful, non-misleading information. This it cannot do. . . . This law chills practitioners' speech in a way that impairs the provision of medical care and may ultimately harm the patient."[2] Yet the state of Florida is continuing to push this issue: Governor Rick Scott recently announced the state's submission of an appeal of Judge Cooke's ruling.[3]

Second, some new laws require physicians to discuss specific practices that may not be necessary or appropriate at the time of a specific encounter with a patient, according to the physician's best clinical judgment. New York legislation that was enacted in 2010 and became effective in early 2011 requires physicians and other health care practitioners to offer terminally ill patients "information and counseling regarding palliative care and end-of-life options appropriate to the patient, including . . . prognosis, risks and benefits of the various options; and the patient's legal rights to comprehensive pain and symptom management."[4] Although the law requires only that the clinician offer to provide information, the Medical Society of the State of New York and others have criticized it for failing to recognize the complexity and uncertainty involved in end-of-life discussions among patients and their families and physicians.[5,6] This is an area in which one size does not fit all and in

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which physicians are best able to determine what discussions with patients and families are necessary or appropriate at a given time. Yet failure to comply with the law can result in fines of up to $5,000 for repeat offenses and a jail term of up to 1 year for willful violations.

Third, still other laws would require physicians to provide — and patients to receive — diagnostic tests or medical interventions whose use is not supported by evidence, including tests or interventions that are invasive and required to be performed even without the patient's consent. In Virginia, a bill requiring women to undergo ultrasonography before having an abortion would have mandated the use of transvaginal ultrasonography for a woman in the very early stages of pregnancy.[7] As the Virginia chapter of the American College of Physicians stressed in a letter urging Governor Bob McDonnell to veto the bill, "opposition to the legislation does not reflect our opinions individually or collectively on the practice of abortion itself," but rather the conviction that "this legislation represents a dangerous and unprecedented intrusion by the Commonwealth of Virginia into patient privacy and that it encroaches on the doctor–patient relationship."[8] A modified bill requiring women to undergo transabdominal rather than transvaginal ultrasonography, which still represents inappropriate legislative intrusion into the patient–physician relationship, was signed by McDonnell in March 2012.[9]

Finally, there are laws limiting the information that physicians can disclose to patients, to consultants in patient care, or both. Four states (Pennsylvania, Ohio, Colorado, and Texas) have passed legislation relating to disclosure of information about exposure to chemicals used in the process of hydraulic fracturing ("fracking").[10] Fracking involves injecting into the ground toxic chemicals such as benzene, toluene, ethylbenzene, and xylene to extract oil and natural gas.[11] Low levels of exposure to those chemicals can trigger headaches, dizziness, and drowsiness; higher levels of exposure can cause cancer. In Pennsylvania, physicians can obtain information about chemicals used in the fracking process that may be relevant to a patient's care, but only after requesting the information in writing and executing a nonstandardized confidentiality and nondisclosure agreement drafted by the drilling companies.[12]

Unfortunately, laws and regulations are blunt instruments. By reducing health care decisions to a series of mandates, lawmakers devalue the patient–physician relationship. Legislators, regrettably, often propose new laws or regulations for political or other reasons unrelated to the scientific evidence and counter to the health care needs of patients. Legislative mandates regarding the practice of medicine do not allow for the infinite array of exceptions — cases in which the mandate may be unnecessary, inappropriate, or even harmful to an individual patient. For example, a patient may already have undergone the test in question or may have specific contraindications to it. Lawmakers would also do well to remember that patient autonomy and individual needs, values, and preferences must be respected.

Laws that specifically dictate or limit what physicians discuss during health care encounters also undermine the patient–physician relationship. Physicians must have the ability and freedom to speak to their patients freely and confidentially, to provide patients with factual information relevant to their health, to fully answer their patients' questions, and to advise them on the course of best care without the fear of penalty.

Federal, state, and local governments have long played valued and important roles in our nation's health care. Various levels of government are appropriately involved in providing essential health care services, licensing health care professionals, protecting public health, determining the safety of drugs and medical devices, and investing in medical education and research. Government plays a particularly important role in ensuring health care access for vulnerable and special-needs populations, including the elderly and disabled (Medicare), the poor (Medicaid), children (the Children's Health Insurance Program), and veterans (the Veterans Health Administration). We are fortunate to have a broad-based and extensive health care system, whose improvement and future excellence depend on a continued partnership between health care professionals and government.

None of the concerns raised above imply that we object to these governmental roles. But we believe that health legislation should focus on public health measures that extend beyond the individual patient and are outside the capacity of individual physicians or patients to control.

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In contrast, government must avoid regulating the content of the individual clinical encounter without a compelling and evidence-based benefit to the patient, a substantial public health justification, or both.

Our objection to legislatively mandated health care decisions does not translate into an argument that physicians can do whatever they want. Physicians are still bound by broadly accepted ethical and professional values.[13] The fundamental principles of respect for autonomy, beneficence, nonmaleficence, and justice dictate physicians' actions and behavior and shape the interactions between patients and their physicians. When physicians adhere to these principles, when patients are empowered to make informed decisions about their care, and when legislators avoid inappropriate interference with the patient–physician relationship, we can best balance and serve the health care needs of individual patients and the broader society.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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ADDENDUM 26

Regulatory Information

"Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices - Information Sheet

Guidance for Institutional Review Boards and Clinical Investigators

Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgement. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner *when the intent is the "practice of medicine"* does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB). However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight.

Investigational Use of Marketed Drugs, Biologics and Medical Devices

The investigational use of approved, marketed products differs from the situation described above. "Investigational use" suggests the use of an approved product in the context of a clinical study protocol [see 21 CFR 312.3(b)]. When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND or IDE may be required. However, according to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

(i) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

(ii) it is not intended to support a significant change in the advertising for the product;

(iii) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];

(v) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and

(vi) it does not intend to invoke 21 CFR 50.24.

For additional information on whether or not an IND or IDE is required in a specific situation, contact:

For DRUG PRODUCTS, including BIOLOGICAL THERAPEUTICS, contact:

The relevant review division – contact information available at http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm075128.htm[1].

If the relevant review division is unknown contact:

Drug Information Branch
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Building 51, Room 2201
Silver Spring, Maryland 20993-0002
301-796-3400

For a BIOLOGICAL BLOOD or VACCINE product:
Office of Communication, Outreach and Development
Center for Biologic Evaluation and Research
Food and Drug Administration
1401 Rockville Pike

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Rockville, Maryland 20852-1448
800-835-4709 or 301-827-1800

For a MEDICAL DEVICE product, contact:
Program Operations Staff
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue, Building 66, Room 1521
Silver Spring, Maryland 20993-0002
301-796-6560

Page Last Updated: 08/10/2011
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
Email FDA

Links on this page:

1. /AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm075128.htm

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April 1982 Volume 12 Number 1

FDA Drug Bulletin

New Angina Drugs

Two calcium channel blockers, nifedipine and verapamil, have been approved for treatment of vasospastic and classical effort-associated angina. These drugs are also referred to as "calcium entry blockers" or "calcium antagonists."

Drugs of this pharmacologic class have some common properties but also have important differences in clinical use.

Both agents inhibit transmembrane ·flux of extracellular calcium into car- · and vascular smooth muscle, and 'vee, in isolated tissues, negative .opic effects, depressed sino-atrial (SA) and atrio-ventricular (AV) node function, and vasodilation. At clinical doses in humans, however, the vascular effects are usually predominant, causing reduced peripheral vascular resistance and lower blood pressure and preventing or reversing coronary spasm. The effects on cardiac tissues are usually less prominent, probably because of afterload reduction and reflex sympathetic responses to vasodilation. In patients with normal cardiac function not on other negatively inotropic drugs, the negative inotropic effects of the drugs are not usually manifested.

In some cases, however, heart failure can be induced or worsened, and particular care must be paid to concomitant use of calcium channel blockers with beta blockers and to use in patients with aortic stenosis, where vasodilation would not be expected to produce significant afterload reduction.

Effects on AV and SA node function are also not prominent *in vivo* with nifedipine, although they can occur with verapamil.

Effectiveness

Verapamil, but not nifedipine, is an effective agent intravenously in interrupting supraventricular tachycardia and slowing the heart rate in atrial fibrillation.

Both drugs are effective in angina due to vasospasm and in chronic stable angina. Current labeling for nifedipine recommends it for use in stable angina only in patients "who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents." This reservation is based on the limited long-term evidence of safety and effective-

more than 1 of every 350 patients were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

No long-term studies have been carried out and there is no recognized reason for long-term use of sucralfate. Specifically, it is not known whether sucralfate can prevent ulcer recurrence. Long-term studies will be needed to assess the possibility of adverse effects associated with long-term use, e.g., effects on absorption of fat-soluble vitamins.

The recommended adult dosage is 1 g four times a day on an empty stomach. Antacids may be prescribed as needed for relief of pain but should not be taken within 30 minutes before or after administration of sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been confirmed by X-ray or endoscopy.

Ritodrine Update

Since the approval of ritodrine (Yutopar) for use in premature labor (see November 1980 and July 1981 *Drug Bulletins*), FDA has been monitoring several areas of concern about the drug's known cardiovascular effects. In light of a number of adverse reaction reports, the labeling of ritodrine has been updated to warn about:

- the need to monitor the patient's state of hydration;
- the possibility of pulmonary edema with or without the concomitant use of corticosteroids, many cases of which seem to be related to overhydration;
- the possible unmasking of occult cardiac disease, the first sign of which may be chest pain.

Ritodrine, a beta$_2$-sympathomimetic drug, may be useful in preterm labor in pregnancies of at least 20 weeks gestation when contraindications have been ruled out.

However, in pregnancies of more than 32 weeks, physicians should carefully weigh the risks and benefits before administering the drug.

When gestational age is in doubt, intrauterine growth retardation should be considered in the differential diagnosis of preterm labor. Among low birth weight infants, about 9 percent may be growth retarded for gestational age. Prolongation of labor beyond term will not correct the growth retardation of these babies.

Initial administration of ritodrine is intravenous. To minimize the risk of hypotension, the patient should be maintained in the left lateral position during infusion and careful attention should be given to her state of hydration. The amount of i.v. fluids administered should be monitored to avoid either circulatory fluid overload (overhydration) or inadequate hydration. An excess sodium load should be avoided in hydrating the patient.[1]

The boxed warning for ritodrine has been amended to read:

> Maternal pulmonary edema has been reported in patients treated with Yutopar, sometimes after delivery. While occurring infrequently, it has occurred more often when patients were treated concomitantly with corticosteroids. Maternal death from this condition has been reported with or without corticosteroids given concomitantly with drugs of this class.
>
> Patients so treated must be closely monitored in the hospital. The patient's state of hydration should be carefully monitored. (See Dosage and Administration.) If pulmonary edema develops during administration, the drug should be discontinued. Edema should be managed by conventional means.
>
> Because cardiovascular responses are common and more pronounced during intravenous administration of Yutopar, cardiovascular effects, including maternal pulse rate and blood pressure and fetal heart rate, should be closely monitored. Observe for premonitory or actual maternal signs and symptoms of pulmonary edema. A persistent high tachycardia (over 140 beats per minute) and/or persistent tachypnea (respiratory rate over 20 per minute) may be signs of impending pulmonary edema with drugs of this class.
>
> Occult cardiac disease may be unmasked with the use of Yutopar. If the patient complains of chest pain, or tightness of chest, the drug should be temporarily discontinued and an ECG should be done as soon as possible.
>
> The drug should not be administered to patients with mild to moderate preeclampsia, hypertension, or diabetes unless the attending physician considers that the benefits clearly outweigh the risks.

References:

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Use of Approved Drugs for Unlabeled Indications

The appropriateness or the legality of prescribing approved drugs for uses not included in their official labeling is sometimes a cause of concern and confusion among practitioners.

Under the Federal Food, Drug, and Cosmetic (FD&C) Act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and which FDA has approved. These are commonly referred to as "approved uses." This means that adequate and well-controlled clinical trials have documented these uses, and the results of the trials have been reviewed and approved by FDA.

The FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

The term "unapproved uses" is, to some extent, misleading. It includes a variety of situations ranging from unstudied to thoroughly investigated drug uses. Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations. Before such advances can be added to the approved labeling, however, data substantiating the effectiveness of a new use or regimen must be submitted by the manufacturer to FDA for evaluation.[1] This may take time and, without the initiative of the drug manufacturer whose product is involved, may never occur. For that reason, accepted medical practice often includes drug use that is not reflected in approved drug labeling.

With respect to its role in medical practice, the package insert is informational only. FDA tries to assure that prescription drug information in the package insert accurately and fully reflects the data on safety and effectiveness on which drug approval is based.

Hepatitis B Vaccine for Use in Selected Populations

An inactivated hepatitis B vaccine Heptavax-B) has been licensed for use the United States. It is intended for ...lected populations at high risk of acquiring hepatitis B, one of three known forms of viral hepatitis. (The others are hepatitis A and non-A non-B hepatitis.)

The vaccine is the first to be made from human blood. Noninfectious antigen is purified from the plasma of asymptomatic human carriers of hepatitis B. After a series of chemical treatments, followed by the addition of alum adjuvant, the vaccine is administered in three intramuscular injections over a 6-month period.

Vaccination is not intended for the general population but is recommended for persons older than 3 months of age who are at increased risk of hepatitis B virus infection. These persons will include health care workers, institutionalized patients, laboratory workers, hemodialysis staff and patients, family contacts of carriers, some military personnel, and persons with numerous sexual partners.

There continues to be a dialogue among government agencies, industry, and the medical community about use of the vaccine in selected high-risk groups. The Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control (CDC), with assistance from representatives of FDA, the National Institutes of Health, and the medical community, has met several times to discuss specifically which population groups should receive this vaccine. The ACIP will meet once more in May of this year to draft final guidelines for use of this vaccine.

Efficacy

In clinical trials, 85 to 96 percent of persons receiving three doses of either 20 mg or 40 mg of vaccine were immune to infection. The duration of protection is presently unknown. However, in clinical trials, vaccine-induced antibodies, shown to provide protection against infection, persisted for at least 24 months in those receiving all three doses and will probably last for at least 5 years. After this time, a booster may be necessary to maintain immunity.

Side effects have been mainly local, mild, and transitory.

Availability

Due to the complexity of the methods used for producing the vaccine, it will be summer or fall of 1982 before the product is generally available from Merck, Sharp & Dohme. This manufacturer can supply complete physician information.

Advice on Limiting Intake of Bonemeal

Due to the unknown but often substantial lead content of individual samples of bonemeal and dolomite, FDA advises practitioners that these substances should be used as little as possible in infants, young children, and pregnant or lactating women.

Bonemeal is used primarily as calcium and/or phosphorus supplements. Bonemeal supplements are usually composed of finely crushed, processed bone and are packaged in powder, capsule, tablet, or wafer form. The source of bone is usually cattle but sometimes also horses. Bone marrow may also be added to this product. All bonemeal products contain lead which originates primarily from the diet of the animals from which the bone is taken. Bone serves as a repository for lead in the body and, in general, the older the animal the more lead in its bones.

Dolomite is a mineral deposit, consisting of calcium-magnesium carbonate with traces of other elements, including lead. Dolomite is used as a calcium and magnesium supplement and, like bonemeal, may be purchased in powder, capsule, tablet, or wafer form.

While a large portion of the small amounts of dietary lead ingested by humans is excreted, some is deposited in the mineral fabric of bone and some goes into soft tissue. Infants and children tend to absorb lead more efficiently than adults. When it is consumed in excess, lead may produce toxic reactions including central nervous system damage, anemia, and abdominal pain. As in animals, the accumulation of lead in human bone increases with age. Additionally, studies with

Hippocratic Oath

I do solemnly vow, to that which I value and hold most dear:

That I will honor the Profession of Medicine, be just and generous to its members, and help sustain them in their service to humanity;

That just as I have learned from those who preceded me, so will I instruct those who follow me in the science and the art of medicine;

That I will recognize the limits of my knowledge and pursue lifelong learning to better care for the sick and to prevent illness;

That I will seek the counsel of others when they are more expert so as to fulfill my obligation to those who are entrusted to my care;

That I will not withdraw from my patients in their time of need;

That I will lead my life and practice my art with integrity and honor, using my power wisely;

That whatsoever I shall see or hear of the lives of my patients that is not fitting to be spoken, I will keep in confidence;

That into whatever house I shall enter, it shall be for the good of the sick;

That I will maintain this sacred trust, holding myself far aloof from wrong, from corrupting, from the tempting of others to vice;

That above all else I will serve the highest interests of my patients through the practice of my science and my art;

That I will be an advocate for patients in need and strive for justice in the care of the sick.

I now turn to my calling, promising to preserve its finest traditions, with the reward of a long experience in the joy of healing.

I make this vow freely and upon my honor.