A Framework for the Medical Profession

Most practicing physicians took some version of the Hippocratic Oath upon graduation from medical school. How relevant is that oath to the practice of medicine today? What are the basic tenets of ethics in medicine? Is there an established framework on which to build an ethical practice?

Chapter in Brief:

- *Although some statements in the original Hippocratic Oath and even the 1964 revision are outdated, ethicists believe that many of the principles and ideas have enduring relevance to physicians and patients today.*
- *Many physician organizations have begun to look anew at medical professionalism in recent years, in the context of all of the outside forces—business, economic, societal, and even geopolitical—that affect or threaten the values associated with the medical profession.*
- *Results of a recent study by U.S. and Australian researchers found that the vast majority—fully 96 percent—of physicians surveyed said that they believe physicians should report an incompetent or impaired colleague through appropriate channels; yet only 45 percent of respondents indicated that they always take such action.*

The oath attributed to Hippocrates in the Fourth Century BC has served for most of the past two millenniums as the basic guide for ethical conduct and a covenant for medical professionalism. Few medical schools still use the original classical version of the oath; but certain of its themes are constant,

including the commitment to patient primacy and privacy and the application and sharing of medical knowledge.

A study by ethicist Robert Orr, MD, and colleagues published in the *Journal of Clinical Ethics* in 1997 examined use of oaths in 157 U.S and Canadian medical schools. The authors' findings were interesting and at times strikingly contradictory. For example, 98 percent of schools administered some form of the oath in 1993 compared with only 26 percent in 1928. At the time the study was conducted, all oaths in use included a commitment to patients, but only 11 percent invoked a deity. In other findings:

- Less than half (43 percent) of oaths in use included a vow that physicians be accountable for their actions.
- Only 14 percent included a prohibition against euthanasia (or an act that could be construed as such).
- Approximately 8 percent included a prohibition against abortion.
- Three percent explicitly prohibited sexual contact between physicians and their patients.

Regardless of how they are structured or the maxims they propose, most oaths in use today share an interesting characteristic: They include no mechanism for monitoring adherence or holding the oath-taking physician accountable for keeping the pledge. That omission, in concert with economic and regulatory realities of modern medical practice, has prompted some physicians to press for either substantial modifications to or abandonment of the oath. In some circles, the Hippocratic Oath is even jokingly referred to as the "hypocritic oath" because the classical version is so incongruous with practice conditions in the 21st Century.

Physicians may find the original oath's maxims out of sync with their day-to-day lives and only marginally useful in guiding relationships with colleagues; yet certain passages concerning patients stand the test of time, maintains Faith T. Fitzgerald, MD, assistant dean of humanities and bioethics at the University of California-Davis Health System in Sacramento.

"I took the Hippocratic Oath, and I have found in retrospect that it gets you off a lot of terrible situations—euthanasia plus or minus, for example," she says. "There are some circumstances in which you very much want to end [patients'] suffering. But

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TOPAMAX® Tablets and TOPAMAX® Sprinkle Capsules are indicated for adults for the prophylaxis of migraine headache. The usefulness of TOPAMAX® in the acute treatment of migraine headache has not been studied.

TOPAMAX® is contraindicated in patients with a history of hypersensitivity to any component of this product.

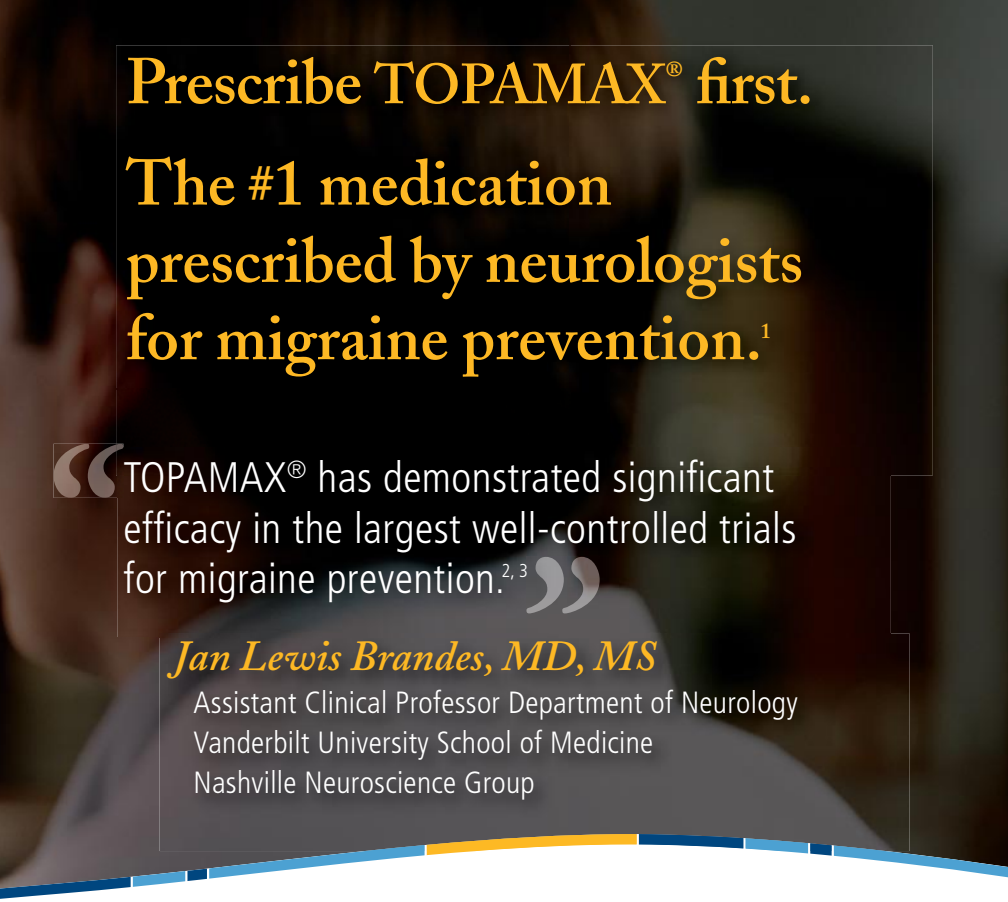
IMPORTANT SAFETY INFORMATION

TOPAMAX® has been associated with serious adverse events, including:

- Hyperchloremic, non-anion gap metabolic acidosis—lowering of bicarbonate levels in the blood. Measurement of baseline and periodic serum bicarbonate is recommended.
- Acute myopia and secondary angle-closure glaucoma—patients should be cautioned to seek medical attention if they experience blurred vision or ocular pain.
- Oligohidrosis and hyperthermia—decreased sweating and increased body temperature, especially in hot weather. The majority of reports have been in children.
- Cognitive/psychiatric side effects including cognitive dysfunction, psychiatric/behavioral disturbances including suicidal thoughts or behavior, and somnolence and fatigue.

Most common adverse events associated with TOPAMAX® 100 mg vs placebo were: paresthesia, 51% vs 6%; anorexia,* 15% vs 6%; fatigue, 15% vs 11%; nausea, 13% vs 8%; diarrhea, 11% vs 4%; weight decrease, 9% vs 1%; taste alteration, 8% vs 1%.

The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be



considered in patients taking combination oral contraceptive products with TOPAMAX®.

Patients should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation.

*Anorexia is defined as loss of appetite.

References: 1. IMS Health, IMS LRx Longitudinal data, TOPAMAX® Monthly Tracking Report, May 2008. Custom Study conducted by IMS Management Consulting. **2.** Brandes JL, Saper JR, Diamond M, et al, for the MIGR-002 Study Group. Topiramate for migraine prevention: a randomized controlled trial. *JAMA*. 2004;291:965-973. **3.** Silberstein SD, Neto W, Schmitt J, Jacobs D, for the MIGR-001 Study Group. Topiramate in migraine prevention: results of a large controlled trial. *Arch Neurol*. 2004;61:490-495.

Please see brief summary of full Prescribing Information on following pages.

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Important
Avoid confusion with Toprol-XL® (metoprolol succinate) by spelling out TOPAMAX® (topiramate) on your prescription. Toprol-XL is a registered trademark of the AstraZeneca group of companies.

TOPAMAX®
(topiramate) Tablets
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October 2008 02M07240ER3

TOPAMAX®
(topiramate)
Tablets

TOPAMAX®
(topiramate capsules)
Sprinkle Capsules

Rx only

Brief Summary of Full Prescribing Information for Migraine. CLINICAL STUDIES FOR OTHER INDICATIONS WILL HAVE DIFFERING ADVERSE EVENTS AND SAFETY CONCERNS. PLEASE SEE FULL PI FOR THIS INFORMATION REGARDING TOPAMAX® FOR EPILEPSY.

INDICATIONS AND USAGE

Migraine: TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated for adults for the prophylaxis of migraine headache. The usefulness of TOPAMAX® in the acute treatment of migraine headache has not been studied.

CONTRAINDICATIONS: TOPAMAX® is contraindicated in patients with a history of hypersensitivity to any component of this product.

WARNINGS: Metabolic Acidosis: Hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Such electrolyte imbalance has been observed with the use of topiramate in placebo-controlled clinical trials and in the post-marketing period. Generally, topiramate-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. Bicarbonate decrements are usually mild-moderate (average decrease of 4 mEq/L at daily doses of 400 mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to values below 10 mEq/L. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs) may be additive to the bicarbonate lowering effects of topiramate. Metabolic acidosis has been observed at doses as low as 50 mg/day. Serum bicarbonate levels have not been systematically evaluated at daily doses greater than 400 mg/day. The incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adults for prophylaxis of migraine was 44% for 200 mg/day, 39% for 100 mg/day, 23% for 50 mg/day, and 7% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was 11% for 200 mg/day, 9% for 100 mg/day, 2% for 50 mg/day, and <1% for placebo. Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients may also reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated. Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). If the decision is made to continue patients on topiramate in the face of persistent acidosis, alkali treatment should be considered. **Acute Myopia and Secondary Angle Closure Glaucoma:** A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving TOPAMAX®. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating TOPAMAX® therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of TOPAMAX® as rapidly as possible, according to the judgment of the treating physician. Other measures, in conjunction with discontinuation of TOPAMAX®, may be helpful. Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequelae including permanent vision loss. **Oligohidrosis and Hyperthermia:** Oligohidrosis (decreased sweating), infrequently resulting in hospitalization, has been reported in association with TOPAMAX® use. Decreased sweating and an elevation in body temperature above normal characterized these cases. Some of the cases were reported after exposure to elevated environmental temperatures. The majority of the reports have been in children. Patients, especially pediatric patients, treated with TOPAMAX® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when TOPAMAX® is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity. **Cognitive/Neuropsychiatric Adverse Events:** Adults: Adverse events most often associated with the use of TOPAMAX® were related to the central nervous system. In adults, the most frequent of these can be classified into three general categories: 1) Cognitive-related dysfunction (e.g., confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, particularly word-finding difficulties); 2) Psychiatric/behavioral disturbances (e.g., depression or mood problems); and 3) Somnolence or fatigue. *Cognitive-Related Dysfunction:* The majority of cognitive-related adverse events were mild to moderate in severity, and they frequently occurred in isolation. Rapid titration rate and higher initial dose were associated with higher incidences of these events. Many of these events contributed to withdrawal from treatment (see **ADVERSE REACTIONS, Table 1**). In the 6-month migraine prophylaxis controlled trials using a slower titration regimen (25 mg/day weekly increments), the proportion of patients who experienced one or more cognitive-related adverse events was 19% for TOPAMAX® 50 mg/day, 22% for 100 mg/day, 28% for 200 mg/day, and 10% for placebo. These dose-related adverse reactions typically began in the titration phase and often persisted into the maintenance phase, but infrequently began in the maintenance phase. Some patients experienced a recurrence of one or more of these cognitive adverse events and this recurrence was typically in the titration phase. A relatively small proportion of topiramate-treated patients experienced more than one concurrent cognitive adverse event. The most common cognitive adverse events occurring together included difficulty with memory along with difficulty with concentration/attention, difficulty with memory along with language problems, and difficulty with concentration/attention along with language problems. Rarely, topiramate-treated patients experienced three concurrent cognitive events. *Psychiatric/Behavioral Disturbances:* Psychiatric/behavioral disturbances (depression or mood problems) were dose-related for both the epilepsy and migraine populations. In the double blind phases of clinical trials with topiramate in approved and investigational indications, suicide attempts occurred at a rate of 3/1000 patient years (13 events/3999 patient years) on topiramate versus 0 (0 events/1430 patient years) on placebo. One completed suicide was reported in a bipolar disorder trial in a patient on topiramate. *Somnolence/Fatigue:* Fatigue and somnolence were dose-related and more common in the titration phase.

PRECAUTIONS: Hyperammonemia and Encephalopathy Associated with Concomitant Valproic Acid Use: Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or

cognitive function with lethargy or vomiting. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction. It is not known if topiramate monotherapy is associated with hyperammonemia. Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, an interaction of topiramate and valproic acid may exacerbate existing defects or unmask deficiencies in susceptible persons. In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. Kidney Stones: As in the general population, the incidence of stone formation among topiramate treated patients was higher in men. Kidney stones have also been reported in pediatric patients. An explanation for the association of TOPAMAX® and kidney stones may lie in the fact that topiramate is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of TOPAMAX® with other carbonic anhydrase inhibitors or potentially in patients on a ketogenic diet may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided. Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation. Paresthesia: Paresthesia (usually tingling of the extremities), an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX®. Paresthesia was more frequently reported in the monotherapy epilepsy trials and migraine prophylaxis trials versus the adjunctive therapy epilepsy trials. In the majority of instances, paresthesia did not lead to treatment discontinuation. Adjustment of Dose in Renal Failure: The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required in patients with reduced renal function (see **DOSAGE AND ADMINISTRATION** in the full PI). Decreased Hepatic Function: In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased. **Information for Patients:** Patients should be instructed to read the Patient Information before starting treatment with TOPAMAX® and each time their prescription is renewed. Patients taking TOPAMAX® should be told to seek immediate medical attention if they experience blurred vision, visual disturbances or periorbital pain. Patients, especially pediatric patients, treated with TOPAMAX® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation [see **PRECAUTIONS:** Kidney Stones, for support regarding hydration as a preventative measure]. Patients should be warned about the potential for somnolence, dizziness, confusion, difficulty concentrating, and visual effects and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental performance, motor performance, and/or vision. Additional food intake may be considered if the patient is losing weight while on this medication. **Laboratory Tests:** Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended (see **WARNINGS**). In double-blind trials hypokalemia defined as serum potassium decline below 3.5 mmol/L has been observed in 0.4% of subjects treated with topiramate compared to 0.1% of subjects treated with placebo. **Drug Interactions:** *In vitro* studies indicate that topiramate does not inhibit enzyme activity for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 isozymes. **Other Drug Interactions: Digoxin:** In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant TOPAMAX® administration. The clinical relevance of this observation has not been established. **CNS Depressants:** Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants. **Oral Contraceptives:** In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), TOPAMAX® given in the absence of other medications at doses of 50 to 200 mg/day was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, TOPAMAX® (50 mg/day to 800 mg/day) did not significantly affect exposure to NET. Although there was a dose dependent decrease in EE exposure for doses between 200-800 mg/day, there was no significant dose dependent change in EE exposure for doses of 50-200 mg/day. The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TOPAMAX®. Patients taking estrogen containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding. **Hydrochlorothiazide (HCTZ):** A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination. **Metformin:** A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin and topiramate in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean C_{max} and mean $AUC_{0\text{-}12h}$ increased by 18% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with topiramate. Topiramate did not affect metformin t_{max}. The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When TOPAMAX® is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state. **Pioglitazone:** A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate and pioglitazone when administered alone and concomitantly. A 15% decrease in the $AUC_{\tau,ss}$ of pioglitazone with no alteration in $C_{max,ss}$ was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ of the active keto-metabolite. The clinical significance of these findings is not known. When TOPAMAX® is added to pioglitazone therapy or pioglitazone is added to TOPAMAX® therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state. **Lithium:** Multiple dosing of topiramate 100 mg every 12 hrs decreased the AUC and C_{max} of Lithium (300 mg every 8 hrs) by 20% (N=12, 6 M; 6 F). **Haloperidol:** The pharmacokinetics of a single dose of haloperidol (5 mg) were not affected following multiple dosing of topiramate (100 mg every 12 hr)

in 13 healthy adults (6 M, 7 F). **Amitriptyline:** There was a 12% increase in AUC and C_{max} for amitriptyline (25 mg per day) in 18 normal subjects (9 male; 9 female) receiving 200 mg/day of topiramate. Some subjects may experience a large increase in amitriptyline concentration in the presence of topiramate and any adjustments in amitriptyline dose should be made according to the patient's clinical response and not on the basis of plasma levels. **Sumatriptan:** Multiple dosing of topiramate (100 mg every 12 hrs) in 24 healthy volunteers (14 M, 10 F) did not affect the pharmacokinetics of single dose sumatriptan either orally (100 mg) or subcutaneously (6 mg). **Risperidone:** There was a 25% decrease in exposure to risperidone (2 mg single dose) in 12 healthy volunteers (6 M, 6 F) receiving 200 mg/day of topiramate. Therefore, patients receiving risperidone in combination with topiramate should be closely monitored for clinical response. **Propranolol:** Multiple dosing of topiramate (200 mg/day) in 34 healthy volunteers (17 M, 17 F) did not affect the pharmacokinetics of propranolol following daily 160 mg doses. Propranolol doses of 160 mg/day in 39 volunteers (27M, 12F) had no effect on the exposure to topiramate at a dose of 200 mg/day of topiramate. **Dihydroergotamine:** Multiple dosing of topiramate (200 mg/day) in 24 healthy volunteers (12 M, 12 F) did not affect the pharmacokinetics of a 1 mg subcutaneous dose of dihydroergotamine. Similarly, a 1 mg subcutaneous dose of dihydroergotamine did not effect the pharmacokinetics of a 200 mg/day dose of topiramate in the same study. **Others:** Concomitant use of TOPAMAX®, a carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided. **Drug/Laboratory Tests Interactions:** There are no known interactions of topiramate with commonly used laboratory tests. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300 mg/kg, was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. Plasma exposures in mice receiving 300 mg/kg were approximately 0.5 to 1 times steady-state exposures measured in patients receiving topiramate monotherapy at the recommended human dose (RHD) of 400 mg, and 1.5 to 2 times steady-state topiramate exposures in patients receiving 400 mg of topiramate plus phenytoin. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg (approximately 3 times the RHD on a mg/m^2 basis). Topiramate did not demonstrate genotoxic potential when tested in a battery of *in vitro* and *in vivo* assays. Topiramate was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay; it did not increase unscheduled DNA synthesis in rat hepatocytes *in vitro;* and it did not increase chromosomal aberrations in human lymphocytes *in vitro* or in rat bone marrow *in vivo.* No adverse effects on male or female fertility were observed in rats at doses up to 100 mg/kg (2.5 times the RHD on a mg/m^2 basis). **Pregnancy: Pregnancy Category C.** Topiramate has demonstrated selective developmental toxicity, including teratogenicity, in experimental animal studies. When oral doses of 20, 100, or 500 mg/kg were administered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. The low dose is approximately 0.2 times the recommended human dose (RHD=400 mg/day) on a mg/m^2 basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain. In rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 2.5, 30, and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with 400 mg/kg (10 times the RHD on a mg/m^2 basis) or greater during the organogenesis period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (0.5 times the RHD on a mg/m^2 basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater. In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 120 mg/kg orally during organogenesis), embryo/fetal mortality was increased at 35 mg/kg (2 times the RHD on a mg/m^2 basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m^2 basis). Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg and above. When female rats were treated during the latter part of gestation and throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20, and 200 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (5 times the RHD on a mg/m^2 basis) and reductions in pre- and/or postweaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m^2 basis) and above. Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg or greater. In a rat embryo/fetal development study with a postnatal component (0.2, 2.5, 30, or 400 mg/kg during organogenesis; noted above), pups exhibited delayed physical development at 400 mg/kg (10 times the RHD on a mg/m^2 basis) and persistent reductions in body weight gain at 30 mg/kg (1 times the RHD on a mg/m^2 basis) and higher. There are no studies using TOPAMAX® in pregnant women. TOPAMAX® should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. In post-marketing experience, cases of hypospadias have been reported in male infants exposed in utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established. **Labor and Delivery:** In studies of rats where dams were allowed to deliver pups naturally, no drug-related effects on gestation length or parturition were observed at dosage levels up to 200 mg/kg/day. The effect of TOPAMAX® on labor and delivery in humans is unknown. **Nursing Mothers:** Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive secretion of topiramate into breast milk. Since many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants to TOPAMAX® is unknown, the potential benefit to the mother should be weighed against the potential risk to the infant when considering recommendations regarding nursing. **Pediatric Use:** Topiramate is associated with metabolic acidosis. Chronic untreated metabolic acidosis in pediatric patients may cause osteomalacia/rickets and may reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated (see **WARNINGS**). Safety and effectiveness in pediatric patients have not been established for the prophylaxis treatment of migraine headache. **Geriatric Use:** In clinical trials, 3% of patients were over 60. No age related difference in effectiveness or adverse effects were evident. However, clinical studies of topiramate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Dosage adjustment may be necessary for elderly with impaired renal function (creatinine clearance rate ≤ 70 mL/min/1.73 m^2) due to reduced clearance of topiramate (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION** in the full PI). **Race and Gender Effects:** Evaluation of effectiveness and safety in clinical trials has shown no race or gender related effects.

ADVERSE REACTIONS: The data described in the following section were obtained using TOPAMAX® (topiramate) Tablets. **Migraine:** In the four multicenter, randomized, double-blind, placebo-controlled, parallel group migraine prophylaxis clinical trials, most of the adverse events with topiramate were mild or moderate in severity. Most adverse events occurred more frequently during the titration period than during the maintenance period. Table 1 includes those adverse events reported for patients in the placebo-controlled trials where the incidence rate in any topiramate treatment group was at least 2% and was greater than that for placebo patients.

Table 1: Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Migraine Trials Where Rate Was ≥ 2% in Any Topiramate Group and Greater than the Rate in Placebo-Treated Patients.[a] **Body System/**Adverse Event followed by Placebo (N=445) first, TOPAMAX® Dosage (mg/day) 50 (N=235) second, 100 (N=386) third, 200 (N=514) fourth. **Body as a Whole – General Disorders:** Fatigue 11, 14, 15, 19; Injury 7, 9, 6, 6; Asthenia 1, <1, 2, 2; Fever 1, 1, 1, 2; Influenza-Like Symptoms <1, <1, <1, 2; Allergy <1, 2, <1, <1; **Central & Peripheral Nervous System Disorders:** Paresthesia 6, 35, 51, 49; Dizziness 10, 8, 9, 12; Hypoaesthesia 2, 6, 7, 8; Language Problems 2, 7, 6, 7; Involuntary Muscle Contractions 1, 2, 2, 4; Ataxia <1, 1, 2, 1; Speech Disorders/Related Speech Problems <1, 1, <1, 2; **Gastro-Intestinal System Disorders:** Nausea 8, 9, 13, 14; Diarrhea 4, 9, 11, 11; Abdominal Pain 5, 6, 6, 7; Dyspepsia 3, 4, 5, 3; **Gastro-Intestinal System Disorders:** Dry Mouth 2, 2, 3, 5; Vomiting 2, 1, 2, 3; Gastroenteritis 1, 3, 3, 2; **Hearing and Vestibular Disorders:** Tinnitus 1, <1, 1, 2; **Metabolic and Nutritional Disorders:** Weight Decrease 1, 6, 9, 11; Thirst <1, 2, 2, 1; **Musculoskeletal System Disorders:** Arthralgia 2, 7, 3, 1; **Neoplasms:** Neoplasm NOS <1, 2, <1, <1; **Psychiatric Disorders:** Anorexia 6, 9, 15, 14; Somnolence 5, 8, 7, 10; Difficulty with Memory NOS 2, 7, 7, 11; Difficulty with Concentration/Attention 2, 3, 6, 10; Insomnia 5, 6, 7, 6; Anxiety 3, 4, 5, 6; Mood Problems 2, 3, 6, 5; Depression 4, 3, 4, 6; Nervousness 2, 4, 4, 4; Confusion 2, 2, 3, 4; Psychomotor Slowing 1, 3, 2, 4; Libido Decreased 1, 1, 1, 2; Aggravated Depression 1, 1, 2, 2; Agitation 1, 2, 2, 1; Cognitive Problems NOS 1, <1, 2, 2; **Reproductive Disorders, Female:** Menstrual Disorder 2, 3, 2, 2; **Reproductive Disorders, Male:** Ejaculation Premature 0, 3, 0, 0; **Resistance Mechanism Disorders:** Viral Infection 3, 4, 4, 3; Otitis Media <1, 2, 1, 1; **Respiratory System Disorders:** Upper Respiratory Tract Infection 12, 13, 14, 12; Sinusitis 6, 10, 6, 8; Pharyngitis 4, 5, 6, 2; Coughing 2, 2, 4, 3; Bronchitis 2, 3, 3, 3; Dyspnea 2, 1, 3, 2; Rhinitis 1, 1, 2, 2; **Skin and Appendages Disorders:** Pruritis 2, 4, 2, 2; **Special Sense Other, Disorders:** Taste Perversion 1, 15, 8, 12; Taste Loss <1, 1, 1, 2; **Urinary System Disorders:** Urinary Tract Infection 2, 4, 2, 4: Renal Calculus 0, 0, 1, 2; **Vision Disorders:** Vision Abnormal <1, 1, 2, 3; Blurred Vision[b] 2, 4, 2, 4; Conjunctivitis 1, 1, 2, 1: [a]Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category. [b]Blurred vision was the most common term considered as vision abnormal. Blurred vision was an included term that accounted for > 50% of events coded as vision abnormal, a preferred term. Of the 1,135 patients exposed to topiramate in the placebo-controlled studies, 25% discontinued due to adverse events, compared to 10% of the 445 placebo patients. The adverse events associated with discontinuing therapy in the topiramate-treated patients included paresthesia (7%), fatigue (4%), nausea (4%), difficulty with concentration/attention (3%), insomnia (3%), anorexia (2%), and dizziness (2%). Patients treated with topiramate experienced mean percent reductions in body weight that were dose-dependent. This change was not seen in the placebo group. Mean changes of 0%, -2%, - 3%, and - 4% were seen for the placebo group, topiramate 50, 100, and 200 mg groups, respectively. Table 2 shows adverse events that were dose-dependent. Several central nervous system adverse events, including some that represented cognitive dysfunction, were dose-related. The most common dose-related adverse events were paresthesia, fatigue, nausea, anorexia, dizziness, difficulty with memory, diarrhea, weight decrease, difficulty with concentration/attention, and somnolence.

Table 2: Incidence (%) of Dose-Related Adverse Events From Placebo-Controlled, Migraine Trials.[a] Adverse Event followed by Placebo (N=445) first, TOPAMAX® Dosage (mg/day) 50 (N=235) second, 100 (N=386) third, 200 (N=514) fourth. Paresthesia 6, 35, 51, 49; Fatigue 11, 14, 15, 19; Nausea 8, 9, 13, 14; Anorexia 6, 9, 15, 14; Dizziness 10, 8, 9, 12; Weight decrease 1, 6, 9, 11; Difficulty with Memory NOS 2, 7, 7, 11; Diarrhea 4, 9, 11, 11; Difficulty with Concentration/Attention 2, 3, 6, 10; Somnolence 5, 8, 7, 10; Hypoaesthesia 2, 6, 7, 8; Anxiety 3, 4, 5, 6; Depression 4, 3, 4, 6; Mood Problems 2, 3, 6, 5; Dry Mouth 2, 2, 3, 5; Confusion 2, 2, 3, 4; Involuntary Muscle Contractions 1, 2, 2, 4; Abnormal Vision <1, 1, 2, 3; Renal Calculus 0, 0, 1, 2. [a]The incidence rate of the adverse event in the 200 mg/day group was ≥ 2% than the rate in both the placebo group and the 50 mg/day group.

Other Adverse Events Observed During Migraine Clinical Trials: Topiramate, for the treatment of prophylaxis of migraine headache, has been administered to 1,367 patients in all clinical studies (includes double-blind and open-label extension). During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology. The following additional adverse events that were not described earlier were reported by greater than 1% of the 1,367 topiramate-treated patients in the controlled clinical trials: **Body as a Whole:** Pain, chest pain, allergic reaction. **Central & Peripheral Nervous System Disorders:** Headache, vertigo, tremor, sensory disturbance, migraine aggravated. **Gastrointestinal System Disorders:** Constipation, gastroesophageal reflux, tooth disorder. **Musculoskeletal System Disorders:** Myalgia. **Platelet, Bleeding, and Clotting Disorders:** Epistaxis. **Reproductive Disorders, Female:** Intermenstrual bleeding. **Resistance Mechanism Disorders:** Infection, genital moniliasis. **Respiratory System Disorders:** Pneumonia, asthma. **Skin and Appendages Disorders:** Rash, alopecia. **Vision Disorders:** Abnormal accommodation, eye pain. **Postmarketing and Other Experience:** In addition to the adverse experiences reported during clinical testing of TOPAMAX®, the following adverse experiences have been reported worldwide in patients receiving TOPAMAX® post-approval. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: bullous skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), hepatic failure (including fatalities), hepatitis, maculopathy, pancreatitis, pemphigus, and renal tubular acidosis.

DRUG ABUSE AND DEPENDENCE: The abuse and dependence potential of TOPAMAX® has not been evaluated in human studies.

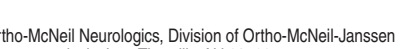
OVERDOSAGE

Overdoses of TOPAMAX® have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbance, blurred vision, diplopia, mentation impaired, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after poly-drug overdoses involving TOPAMAX®.

Topiramate overdose has resulted in severe metabolic acidosis (see **WARNINGS**).

A patient who ingested a dose between 96 and 110 g topiramate was admitted to hospital with coma lasting 20-24 hours followed by full recovery after 3 to 4 days.

In acute TOPAMAX® overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to adsorb topiramate *in vitro*. Treatment should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body.



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having taken an oath, it was a fundamental promise I made as a physician—and the keeping of promises is what it's all about."

Dr. Fitzgerald's view is this: The moral and ethical terrain physicians find themselves in is dauntingly expansive and often tricky to navigate, but they can find their way through challenging situations if they place the patient's interests first and always above their own. "It really means conducting themselves in such a way as to keep the patient's trust, because maintaining that trust cuts right to the heart of things–and it takes care of a lot of other issues along the way," says Dr. Fitzgerald, a renowned educator and ethicist who frequently speaks on physician responsibility to patients and to the profession.

Trust in Doctors

While consumers have become proactive about researching their own health conditions, engaging in self-management, and at times questioning their physician's diagnosis or medical advice, Dr. Fitzgerald explains, most patients and society in general still place tremendous trust in doctors. This is illustrated, Dr. Fitzgerald says, when a mother hands her sick infant "to a white-coated pediatrician she has never met...That's really the degree of trust people have—and it's an awesome, irreducible trust." In exchange, she notes, patients and their families expect physicians to maintain that trust and to embody high standards of conduct.

Maintaining that trust involves *individual* responsibility and *role* responsibility, Dr. Fitzgerald explains, in the face of time constraints and myriad mounting demands from all quarters—patients, insurers, and regulatory entities, to name a few.

"Individual responsibility means keeping your promises that you will be there when necessary, that you will be honest with them and tell the truth, and that you will do everything you can to get the patient in the place where he or she wants to be," Dr. Fitzgerald says.

Role responsibility entails not only maintaining the high moral standards the medical profession vows to uphold, but also acting as needed to stop physicians who don't behave ethically.

"If other doctors are eroding the trust, it's your responsibility to stop them from doing that," Dr. Fitzgerald says. "It's a big

problem, because people never say 'that doctor,' they say 'those doctors.' Every time one of them misbehaves, it taints all of us and erodes the trust that allows us to be doctors."

Keith Brownsberger, MD, an Anchorage, Alaska, infectious disease specialist, has been in practice nearly 40 years and has served on the Alaska state medical board for nine of those years. He says that patients and the general public expect physicians to uphold certain ethical standards. Based on his longtime experience with the disciplinary board, Dr. Brownsberger says those expectations have not changed markedly—despite the sometimes negative portrayal of the medical profession's ethics on television and in movies. This is a message he thinks younger physicians especially need to hear.

"I think the public still holds physicians to a high standard, and many young doctors will learn the hard way that the general public doesn't view them as TV doctors," Dr. Brownsberger says. "Some may think they can test the waters and get away with things–but they may find themselves before the state medical board."

Deep Ethical Roots

Sarasota, Fla., internist Frederick Turton, MD, former chair of the American College of Physicians ethics committee, recently revisited both the classical and oft-cited "modern" (1964) version of the oath to see how they hold up now. "I swore to the modern one when I was in medical school, but I was surprised

The Hippocratic Oath, Classical Version: Archaic but Applicable?

Some sections of the original, classical version of the Hippocratic Oath, which dates to the Fourth Century BC, come across as impossibly archaic today. Certain age-old basics, however—especially regarding patient primacy and privacy, and physician-patient relations—hold up well in modernity, many medical ethicists contend.

I swear by Apollo Physician and Asclepius and Hygieia and Panaceia and all the gods and goddesses, making them my witnesses, that I will fulfill according to my ability and judgment this oath and this covenant:

- To hold him who has taught me this art as equal to my parents and to live my life in partnership with him, and if he is in need of money to give him a share of mine, and to regard his offspring as equal to my brothers in male lineage and to teach them this art—if they desire to learn it—without fee and covenant; to give a share of precepts and oral instruction and all the other learning to my sons and to the sons of him who has instructed me and to pupils who have signed the covenant and have taken an oath according to the medical law, but no one else.
- I will apply dietetic measures for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice.
- I will neither give a deadly drug to anybody who asked for it, nor will I make a suggestion to this effect. Similarly I will not give to a woman an abortive remedy. In purity and holiness I will guard my life and my art.
- I will not use the knife, not even on sufferers from stone, but will withdraw in favor of such men as are engaged in this work.
- Whatever houses I may visit, I will come for the benefit of the sick, remaining free of all intentional injustice, of all mischief and in particular of sexual relations with both female and male persons, be they free or slaves.
- What I may see or hear in the course of the treatment or even outside of the treatment in regard to the life of men, which on no account one must spread abroad, I will keep to myself, holding such things shameful to be spoken about.
- If I fulfill this oath and do not violate it, may it be granted to me to enjoy life and art, being honored with fame among all men for all time to come; if I transgress it and swear falsely, may the opposite of all this be my lot.

to see how well the [original] Hippocratic Oath covers the important issues," Dr. Turton says. He is also impressed that "social justice" was mentioned so early in the history of medicine. "Both versions actually cover the four principles of bioethics that we rely on a lot—beneficence, non-malfeasance, patient autonomy, and social justice—well."

However, even in the modern version, there are inherent discrepancies and incongruence with the current practice environment, Dr. Turton points out. "The classical version contains no reference to conflicts of interest or the payment system," he says. The modern version's requirement that physicians avoid "the twin traps of overtreatment and therapeutic nihilism" is both especially pertinent and problematic now, he added.

"So much of physicians' behavior [today] is generated by fear of malpractice, and litigation is a cloud that follows us wherever we go," Dr. Turton says. "And it's dealt with by over-ordering, over-testing, and over-treating, often just to cover the doctor." That in turn may violate the ethics principle of non-malfeasance, he continues, in that "everything we do has a potential cost to the patient—a financial one, a risk [of injury], or even a risk of misinformation." And if physicians order tests that are likely unnecessary, primarily for their own protection and not the patients' purposes, that counters the principle of patient-centeredness, he says. Dr. Turton acknowledges these issues are complicated ones with a lot of "gray areas."

The modern oath contains sections that many ethicists think are as meaningful now as they were when it was written in 1964, even if the healthcare delivery system presents some different challenges. Dr. Turton points to two particular passages—"above all, I must not play God" and "I must remember that I do not treat a fever [or] a cancerous growth … but a sick human being, whose illness may affect the person's family and economic stability."

"It gets down to patient autonomy and the need for truth-telling and transparency," Dr. Turton says. The latter passage is a reminder of physicians' collective responsibility to take care of everyone, including the uninsured, in an equitable manner that supports human dignity. That ethical requirement is challenged today, Dr. Turton acknowledges, by conflicts that arise when a

Hippocratic Oath, Modern Version: Is Moral Message Meaningful?

Crafted in 1964 by Louis Lasagna, MD, then academic dean of the School of Medicine at Tufts University in Massachusetts, the modern version of the original Hippocratic Oath is still uttered by many U.S. medical school students upon their graduation. Increasingly, however, institutions are modifying the oath. Here is Dr. Lasagna's version:

- I swear to fulfill, to the best of my ability and judgment, this covenant: I will respect the hard-won scientific gains of those physicians in whose steps I walk, and gladly share such knowledge as is mine with those who are to follow.
- I will apply, for the benefit of the sick, all measures which are required, avoiding those twin traps of overtreatment and therapeutic nihilism.
- I will remember that there is art to medicine as well as science, and that warmth, sympathy, and understanding may outweigh the surgeon's knife or the chemist's drug.
- I will not be ashamed to say "I know not," nor will I fail to call in my colleagues when the skills of another are needed for a patient's recovery.
- I will respect the privacy of my patients, for their problems are not disclosed to me that the world may know. Most especially must I tread with care in matters of life and death. If it is given me to save a life, all thanks. But it may also be within my power to take a life; this awesome responsibility must be faced with great humbleness and awareness of my own frailty. Above all, I must not play at God.
- I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person's family and economic stability. My responsibility includes these related problems, if I am to care adequately for the sick.
- I will prevent disease whenever I can, for prevention is preferable to cure.
- I will remember that I remain a member of society, with special obligations to all my fellow human beings, those sound of mind and body as well as the infirm.
- If I do not violate this oath, may I enjoy life and art, respected while I live and remembered with affection thereafter. May I always act so as to preserve the finest traditions of my calling and may I long experience the joy of healing those who seek my help.

current patient loses insurance and health plan contracts dictate how physicians interact with patients regarding copayments and billing, and reimbursement remains poor for primary care.

"I think that this is on everyone's mind now, and it doesn't matter where you are. If your patient becomes uninsured and can't afford you, the physician has to make some very basic decisions," Dr. Turton says, "and there's also the question of whose responsibility it is to care for the uninsured." There is a sense that physicians have assumed a disproportionate burden for caring for uninsured to physicians' own economic detriment, in essence "letting the government off the hook" for what is a societal issue.

Medical Professionalism Under Challenge

Perhaps the most timely ethical area is medical professionalism, which is the basis for physicians' contract with society. Many physician organizations have begun to look anew at the issue in recent years, in the context of all of the outside forces—business, economic, societal, and even geopolitical—that affect or even threaten the values of professionalism today.

Changing market conditions, constant shifts in the healthcare delivery system, and the proliferation of technology are chief among those forces, but physicians are also experiencing ethical challenges because of issues such as terrorism and globalization.

The American Medical Association (AMA) and the American College of Physicians (ACP) are among the groups that have modified policies, position statements, and guidance in recent years to reflect those challenges to medical professionalism. ACP has been very proactive in this regard, as its members cite increasing difficulties maneuvering in what some physicians view as an ethical minefield today, according to Lois Snyder, JD, director of the ACP's Center for Ethics & Professionalism.

"As a general theme, we're looking at the issues that appear to challenge physicians' focus on the patient now—from external pressures to incentive programs, to technology that may actually interfere with the physician-patient relationship," Ms. Snyder observed.

Certain issues have been pressing enough to warrant modifications to ACP's ethics manual. In other cases, the organization

has responded to emerging ethical challenges (such as physician involvement in detainee interrogation activities in military settings) by drafting targeted position statements.

To both recognize and combat current market and other forces that threaten physicians' sense of and views on medical professionalism, three leading organizations—the American Board of Internal Medicine, the ACP Foundation, and the European Federation of Internal Medicine launched the Medical Professionalism Project in 2002. The participants proposed the following principles as the basis for renewed professionalism:

Principle of primacy of patient welfare. This principle is based on a dedication to serving the interest of the patient. Altruism contributes to the trust that is central to the physician-patient relationship. Market forces, societal pressures, and administrative exigencies must not compromise this principle.

Principle of patient autonomy. 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.

Principle of social justice. The medical profession must promote justice in the healthcare system, including the fair distribution of healthcare resources. Physicians should work actively to eliminate discrimination in healthcare, whether based on race, gender, socioeconomic status, ethnicity, religion, or any other social category.

For complete text and details on accompanying professional responsibilities and commitments, go to *www.abim foundation.org/ professionalism/charter.shtm*.

Harvard Medical School researcher Eric Campbell, PhD, who is an associate professor in the Institute for Health Policy at Massachusetts General Hospital, defines the concept of medical professionalism as "a set of normative attitudes and behaviors that people expect physicians to exhibit.

"It's really that simple. But the important part is that we all expect this professional congruence—that doctors' attitudes will match their behaviors," Dr. Campbell explains, "and research shows that's not the case." In some situations, the discrepancy

may be due to a character issue, an ethical lapse, or a personality trait. In others, it may be outside influences—such as those Dr. Turton cites—that come between physicians and the values the profession collectively promises to uphold.

"For example, if I believe that doctors should provide care to people regardless of their ability to pay, some physicians may not be able to do that if they work for a managed care company," Dr. Campbell says. He adds that even a cursory look at the generally accepted domains of professionalism, listed below, presents a compelling picture of the conflicts and challenges physicians may encounter daily:

- To distribute resources in a fair way
- To increase scientific knowledge
- To be honest with patients
- To improve access to care
- To improve quality of care
- To maintain professional competence
- To protect patient confidentiality
- To manage conflicts of interest
- To engage in self-regulation
- To maintain appropriate relationship with patients

"There are ethical issues in each and every one of these domains," Dr. Campbell says, as well as widely differing opinions on the extent of physicians' associated responsibilities. "We need a better understanding of professionalism and the issues, to understand the disconnect between attitudes and behavior."

Often it is not a character issue that becomes the chief source of dissonance between expected norms and physicians' behavior, but the environment in which they find themselves. "It might be characteristics of the hospital or even characteristics of the market that influence individuals differently. And when those exist, you have an immediate ethical issue," Dr. Campbell observes. "Professionalism is more than the person—it's about the person in a hospital, in a market, in a specialty—and each of these levels has a chance to promote some behaviors and attitudes and not promote others," he says. "And it's very complex."