Weighing Medical Evidence

Physicians practicing EBM must evaluate medical literature, detect bias, assess methodology, determine validity, assess applicability of the information as it applies to the patient, and review the process to improve practice.

Fast Facts

- *Despite the availability of Internet-based and other electronic resources, physicians continue to rely primarily on their colleagues and printed literature for their information. But evidence-based journals and databases can offer a better way to access information.* *Page 66*
- *It can be challenging to find evidence and figure out what information is solid, valid, and trustworthy. Physicians need to be able to assess different types of evidence and look out for bias in the literature.* *Page 79*
- *Using EBM doesn't always lead to a clear answer. But it can lead to a better understanding of the alternatives.* *Page 83*

Before physicians can practice EBM, they must know where to find evidence, how to determine which evidence is applicable, and how to convert the data from abstract evidence to useful information that can be incorporated into their working medical practice.

One might expect this would be taught in medical school; but most medical schools do not require courses in interpreting clinical trials, says Kay Dickersin, Ph.D., Director of the Johns Hopkins Center for Clinical Trials and Director of the U.S. Cochrane Center based at Johns Hopkins Bloomberg School of Public

Health in Baltimore, Md.

There is no standardization and no formal way of teaching evidence-based health care, epidemiology, and biostatistics during residency or medical school while students are a captive audience, Dr. Dickersin says. Some schools offer courses, but often they are taught by clinicians without formal training, or they are condensed into a one-month course.

Dr. Dickersin believes these courses should be required. Medical students may initially resist having to take these courses when what they really want to do is see patients, she admits. But a couple of years later, when those physicians are seeing patients and needing to find evidence, they realize they should have paid attention to those unwanted courses.

Another area that's lagging behind is the development of standardized formats for reporting studies. Standards would help physicians by improving the writing quality of papers and making it easier for clinicians to digest the information. The CONSORT statement (*www.consort-statement.org*), a checklist for reporting randomized controlled trials, was endorsed by several leading journals in 2001. This checklist has provided an evidence-based approach to standardizing the reporting of randomized trials, Dr. Dickersin says, "and now we're moving toward other types of standardizations" such as STROBE (**ST**rengthening the **R**eporting of **OB**servational studies in **E**pidemiology) for observational studies (*www.strobe-statement.org*), QUORUM for meta-analyses of randomized trials (*www.consort-statement.org/quorum.pdf*), and STARD for diagnostic studies (*www.consort-statement.org/stardstatement.htm*).

Four Key Questions

Diana Mason, R.N., Ph.D., editor-in-chief of the *American Journal of Nursing,* recommends the following four key questions for all practitioners to use in assessing evidence:

- What is adequate evidence?
- Do we have adequate evidence?
- How much bias is there in the evidence we have?
- What are we missing? What does this evidence *not* tell us?

Helping Change the Cycle of Migraine

A RICHER UNDERSTANDING OF PATIENTS' MIGRAINE IMPAIRMENT

The renowned Diamond Headache Clinic recently hosted a meeting featuring the results of the landmark American Migraine Communication study (AMCS). The study revealed that, during office visits for migraines, patients heard mostly closed-ended or short-answer questions (91%), which prompted limited responses.[1] Such questions may tell you about frequency and severity but may fall short in clarifying the patient's total level of impairment due to migraine.

AMCS reveals prevention is often overlooked

Despite the fact that many patients met the American Migraine Prevalence and Prevention study criteria for prevention, discussions were initiated in only 50% of the office visits.[1]

50%

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.

COULD LEAD TO BETTER INFORMED TREATMENT DECISIONS.[1]

Improving Communication Is Important to a Broader Assessment

Open-ended questions can help you gain a richer understanding of your patients' impairment during and *in between* their attacks.

The study showed that most patients gave brief yet informative responses to questions and prompts like these: [1]

- "How do migraines make you feel—even when you aren't having one?"
- "Describe the total impact migraines have on your work, family, or social life."

A Subtle Communication Shift Can Help Make a Difference

You may find asking open-ended questions leads to a broader assessment of migraine impairment, and the disruption, disability, and frustration that can come with it. In fact, your patients' level of impairment may require a different treatment option.

Finding out if your patients are feeling trapped in a cycle of suffering, treating and worrying may open up an opportunity to discuss the need for preventive therapy. TOPAMAX can help stop migraines before they start—so your patients can get fewer of them.[2,3] TOPAMAX offers proven efficacy and is the #1 prescribed brand for migraine prevention in the U.S. [4]

When evaluating migraine, consider using open-ended questions to assess the total degree of migraine impairment. Then talk about the possibility of preventive therapy with TOPAMAX.

The Migraine Discussion Continues

Look for the next installment of *Helping Change the Cycle of Migraine*, in which we'll continue to explore important topics regarding the migraine patient and strategies to help enhance patient care.

ORTHO-McNEIL NEUROLOGICS, Inc.

Together Rx Access

Together Rx Access is a trademark of Together Rx Access, LLC.

TOPAMAX® (topiramate) Tablets

www.TOPAMAX.com

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.

Please see brief summary of Prescribing Information on following page.

℞

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.

References: 1. Hahn SR, Nelson M, Lipton RB. Provider-patient migraine discussions: Results of American Migraine Communication study (AMCS). Poster presented at: 58th American Academy of Neurology Annual Meeting, April 1–8, 2006; San Diego, California. 2. 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. 3. 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. 4. IMS Data. July 2006.

October 2006

02M802

TOPAMAX®
(topiramate)
Tablets

TOPAMAX®
(topiramate capsules)
Sprinkle Capsules

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 encephalography 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**). 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 taking TOPAMAX® should be told to seek immediate medical attention if they experience blurred vision 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, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance. 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**). **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_{0-12h} 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 $AUC_{t,ss}$ 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 $AUC_{t,ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max,ss}$ and $AUC_{t,ss}$ 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 topiramate 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, 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.

ORTHO-McNEIL NEUROLOGICS, INC.

ORTHO-McNEIL NEUROLOGICS, INC.
Titusville, NJ 08560

Revised June 2005 7517113MB

Finding Evidence

It can be difficult to winnow out the best information amid the ever-increasing blizzards of data. New evidence-based journals and databases can help the physician with this task, but physicians may not be taking advantage of their availability.

In a 2005 review of the international literature published in the *Journal of the Medical Library Association,* researchers found that physicians' sources of information had changed little since a previous review in 1992. Physicians rely primarily on two sources: their colleagues and printed literature, including journals and books. This practice hasn't changed much over the years, even though physicians have greater access to more resources, including Internet-based and other electronic databases. "One of the main difficulties primary care physicians report when looking for electronic information is the amount of time it takes," the authors state—time that isn't directly billable. The researchers conclude: "Because searching the literature might be faster, cheaper, and sometimes more useful than other procedures, such as a blood test or scan, it has been advocated that medical insurance cover this type of 'procedure.'"

Paul Chrisp, Ph.D., Editor-in-chief of the journal *Core Evidence,* estimates there are some 82 randomized controlled trials published every day and says given the physician's resources and time, it's impossible to keep up with all of them. That's why journals like *Core Evidence* were created, to serve as a single source to provide to the physician the best evidence on a given topic. "What we do is review all of the published evidence, we evaluate it and its strength, its weight, and its reliability, and we come to conclusion as to how effective new drugs are in the diseases in which they're indicated," Dr. Chrisp says.

"We try to choose what we believe to be the most important new drugs, using an international perspective to focus on the drugs that are most likely to have a major impact on clinical care and on patients' lives," Dr. Chrisp explains. "We differ from other review journals in three ways. First, we focus on the outcomes that are important to doctors and patients," going beyond the pharmacology and science to "the things that matter for patients" such as a disability, symptom relief, or quality of life. "The second difference we look at is the emerging evidence as

drugs go through development." The journal prepares preliminary reviews that assess the potential impact of a drug in clinical trials. The review also notes what criteria the drug will have to meet for widespread use by physicians and managed-care organizations.

"The third differentiator is our editorial process," Dr. Chrisp says. "We deploy a range of industry-standard methodologies to look at the literature."

The knowledge base that physicians use to practice medicine is constantly evolving as new evidence is added to amplify, clarify, modify, nullify, or verify the old. Research papers that used to take months between submission to a journal and publication are now appearing in print faster. Leonard A. Levin, M.D., Ph.D., professor of ophthalmology at the University of Wisconsin at Madison, attributes this change to advances in technology and communications that journalist and author Thomas L. Friedman has dubbed "the flattening of the world." In his December 2006 *Archives of Ophthalmology* editorial entitled "The Flattening of Medical Publishing," Dr. Levin writes, "There has been a dramatic improvement in the time from manuscript submission to publication." In 2003, he says, authors could expect their papers to take more than 100 days from submission to "first decision," which he notes was usually either a request for revision or a rejection. "In contrast, during the first 7 months of 2006, it took the average manuscript only 29 days, a 71% decrease," Dr. Levin writes.

In 2003, Dr. Levin says, authors could expect their papers to take more than 100 days from submission to "first decision," which he notes was usually either a request for revision or a rejection. "In contrast, during the first 7 months of 2006, it took the average manuscript only 29 days, a 71% decrease."

On the plus side, speeding the publication process means physicians have access to important and current information faster than ever. On the minus side, this increased speed adds to the physician's burden to keep up with the newest developments and most current information as it becomes available.

While modern technologies have accelerated the creation and delivery of medical information to speeds undreamed of in the

past, the problem that physicians face in keeping up with the avalanche is not new. As far back as the year 1872, the problem was noted by German surgeon Bernhard von Langenbeck, who said, "It has become increasingly difficult to keep abreast of and to assimilate the investigative reports which accumulate day after day." He said his colleague "was ill at ease because he felt unable to control even the area of his own discipline; one suffocates, he once told me, through exposure to the massive body of rapidly growing information."

The sources physicians use should allow them to see where the information comes from and how it has been processed so "you can understand how the results are arrived at," says Charles Young, M.R.C.P., editor of *BMJ Clinical Evidence*. There is no shortage of information that tells the physician what to do; but the "why" behind the instruction is not always obvious. He adds, "I'm a practicing emergency physician, and that always makes me nervous." Before he takes any step in treating a patient, Dr. Young says, "I have to understand why I'm doing it."

Applying EBM In Prostate Cancer

Clifford Dacso, M.D., professor of medicine, chief of general medicine and vice-chair for clinical affairs in the Department of Medicine at Baylor College of Medicine in Houston, Texas, is working on a prototype of a prostate cancer decision-making model, which he presented at the Society for Medical Decision Making in 2006.

A man with early prostate cancer has essentially four options, Dr. Dacso says "The only thing he knows about those four options is that they have been tested on people who are not him. You can only have early prostate cancer once. It is a one-time decision. Once you have made a decision as to what intervention you wish to choose, it precludes the other [choices]; so that initial decision is very important. You have got to make that decision based on the best available evidence as it applies to you, taking into account your own preferences. We have made up a model to allow people to do that – to say I want to put my preference in here and test what the likely outcome is going to be…to test it without having an operation." His team has been working on it for over a year and has not put the prototype through an Internal Review Board, so it's "not ready for prime time" yet, Dr. Dacso says.

As a practical matter, physicians cannot review all the literature that may apply to a particular patient's problem. There must be some selection process, says medical oncologist Barnett Kramer, M.D., M.P.H., Associate Director for Disease Prevention at the National Institutes of Health and Director of the Office of Medical Applications Research. "It depends on how much time you have to delve into the question," he says. "Textbooks are very good, but they become outdated pretty quickly; in addition, they often reflect the opinions and perspectives of that author or a very few others for that chapter" and don't include the newest literature, he explains. Given enough time, one could go to the primary literature; "but that, of course, is exhausting, and even that isn't systematic," Dr. Kramer says. "I often find it very useful to go to the evidence-based databases online, read through [them and] see if there are particular papers that get exactly at the patient I am dealing with," he says. Often the database includes a link to retrieve and read the full text immediately.

Using evidence-based databases allows the physician to apply information much more efficiently, Dr. Kramer says. "It is an advantage to the physician and also to the patient because the patient has a physician who is quickly assimilating a huge amount of information," he adds. Granted, that may not be possible for every case, "but once you incorporate that particular fund of knowledge for a clinical situation, then that will stick with you for a while until it becomes outdated," he notes.

Dr. Kramer is a member of the National Cancer Institute Physician Data Query (PDQ) Editorial Board. In this role, he becomes aware of new literature as it appears. "There's a very efficient search engine for the PDQ that scans hundreds of journals every week; so articles that are relevant to a particular question get picked up and discussed by the editorial board monthly," he explains. He also chairs the PDQ Screening and Prevention Board for cancer and says it also does a monthly search of all relevant journals. "These articles are sent out to the various editorial board members, and they flag some for discussion. There's a lot of change. That is just the nature of science that is going on," he says.

Information in Action

But, he adds, "the average clinician certainly wouldn't have time to track" all the developments in every area. That's where the databases come in handy." Even with his expertise in oncology and his role on boards that review this information, Dr. Kramer says he checks the databases frequently to see if anything has changed on recurring clinical questions. "If there's a reoccurring decision or clinical situation that often comes up, I still like to go to the databases just to see that I haven't missed the latest pertinent information," he says.

Not all questions have definitive answers. When the physician has applied EBM and is uncertain, it is important to engage the patient in a dialogue, Dr. Kramer says. "It's a humbling experience, especially in oncology. I think that the practice of oncology reminds us every day to retain our humility." He adds, "I think we need to be trained for uncertainty, trained in the judicious use of diagnostic tests, and [trained to] weigh evidence rather than simply accept what others are doing as definitive."

With so many conditions, so many treatments, and such rapid advancements in health care, everyone should be practicing EBM, says R. Lawrence Van Horn, Ph.D., M.P.H., M.B.A., associate professor of management; faculty director, health care, The Owen Graduate School of Business at Vanderbilt University in Nashville, Tennessee. EBM will allow physicians to "draw upon and implement best practices to improve the quality of care for their patients," he says. Using EBM "will promote higher quality of care, and it can also reduce cost by reducing inappropriate variation" from best practices, he adds.

Dr. Van Horn says, "There is quite a bit of evidence that suggests that all physicians don't approach problems in the same way; and while some degree of variation could be warranted, we see lots of clinically inappropriate variations with patients being treated in ways that are not consistent with the current best practices in medicine as evidenced by the literature and research." The goal should be to eliminate inappropriate variation by consistent adherence to best practices and by following evidence-based strategies for patient care.

"Evidence-based Medicine," Dr. Van Horn explains, "is based on population guidelines. It's not a cookbook that's applied to

every patient; but it's a clinically [based] and evidence-based approach to treating a particular condition, and if there are variations from that treatment approach, well, there's a reason for it. We're not caring for patients just based on the way we might have been trained," he adds, "but rather what is best practice as evidenced by the literature."

One way to apply EBM is to use the tools that bring the evidence into the exam room or to the patient's bedside, like the Framingham Heart Study Risk Assessment Tool that Scott Luria, M.D., associate professor at the University of Vermont College of Medicine in Burlington, uses each day in his practice.

Another way EBM is applied in practice is when physicians are asked to enroll patients in studies. "We are all asked to participate in research almost every day," Dr. Luria says. Several times a week he is asked, "Would you be willing to enroll your patient in this study?" Why? Because, he says, "we as front-line physicians have the patients," and researchers need to enroll patients in trials in order to answer medical questions. So physicians work on both ends of the evidence spectrum—both as providers or producers of evidence and as users or appliers of evidence.

Physicians can work on both ends of the evidence spectrum—both as providers or producers of evidence and as users or appliers of evidence. Physicians have the patients that researchers need to enroll in trials in order to answer medical questions. By informing patients about clinical trials for which they may qualify, physicians can help build the body of evidence that will lead to more effective treatment options.

The Right Tool for the Job

Physicians need to be proactive about research, Dr. Luria says, and they should take advantage of available tools. Physicians also need help weighing the evidence, and many good resources are available to provide that service.

One resource that Dr. Luria uses is Epocrates (*www.epocrates.com*), which he describes as being "like a PDR, a drug resource right on your Palm [handheld computer]; I use it constantly." It is a valuable EBM tool that provides "an impartial breakdown of the meds with their prices and interactions and [is]

a much more useful tool than the PDR itself. It's right there at your fingertips, wherever you are. It is updated every day," he notes. It includes all the formularies, and one also includes herbal therapies. Dr. Luria explains he likes Epocrates because it "shows methods of action, alternatives for that class of drugs that will be covered by the patient's insurance company's formulary, retail cost as well as their cost under the patient's insurance plan." He says he often finds there is an older drug that works much the same way and would be just as effective as a newer one, at a fraction of the price.

Is this a classic evidence-based tool? "Not really," says Dr. Luria, but it does give the physician instant access to objective data, which is more evidence-based than choosing a drug based on what the physician heard from the drug salesman or read in a magazine.

Another evidence-based tool is the Cochrane Collaboration, an international not-for-profit organization that sifts through and synthesizes the evidence from clinical trials and makes that information available through a collection of databases called the Cochrane Library. "I think the Cochrane Collaboration is probably doing some of the best work in terms of reviewing the evidence on a topic and then making recommendations for prac-

A Hard Look at the Evidence

"The bias and the conflicts of interest are just all over the place," says Diana Mason, R.N., Ph.D., editor-in-chief of the *American Journal of Nursing*. "We screen for that, and most of the top-tier medical journals do," but she notes many of the nursing journals do not, nor do some biomedical journals. That means physicians and other practitioners who work with physicians must question the extent to which they can trust what they find in the literature.

She cites the example of an October 4, 2006, *JAMA* report on rapid-response teams. "Everybody is doing rapid response," Dr. Mason says. "It is one of the six interventions that were part of the *100,000 Lives Campaign* that the Institute for Healthcare Improvement did."

The JAMA study looked for research documenting a difference in cardiac arrest or mortality with rapid response teams. But it turned out there was actually very little evidence supporting the deployment

tice based upon that research," says Dr. Mason. "They have people who are very well versed in how to critique research and how to pick it apart, and they have criteria for how to grade the research." She notes the process is very time-consuming. "I think the average clinician doesn't have the time or knowledge" to do that level of review. So the Cochrane Library is a great resource for doctors.

But as Dr. Dickersin (who is Publication Arbiter of the Cochrane Collaboration Steering Group) points out, the key is knowing what types of evidence you might find in the various resources. Dr. Dickersin realizes that "we have been so unclear" about how to find and use information resources. "We have to be very clear that you look in some places for certain types of evidence, and you look in other places for other types of evidence, and they are not all in the same place," she says.

To make EBM really useful, it should be "a real partnership" with physicians, Dr. Dickersin says. "We can't produce the evidence and put it in a format that's good for doctors without their feedback—and it has to be pretty detailed feedback," she adds. "When they say to us, 'We don't have time for the way you're presenting that information' or 'You're not presenting that information in a way we can use,' that is not helpful." She needs to

of rapid response teams, she says. "What they are suggesting is that what the intervention may be more helpful at doing is educating staff on how to detect deterioration in patients and how to intervene early."

She contrasts that study with a solid body of research published in journals such as the *Journal of the American Medical Association* and the *New England Journal of Medicine* that shows that having an adequate R.N. nursing staff is linked to a reduced mortality rate, shorter hospital stays, and lower morbidity from cancer, pneumonia, shock, cardiac arrest, and gastrointestinal bleeds. "If you look at nurse staffing and patient safety intervention," having adequate R.N. nursing staff "is more cost-effective for averting death than things like thrombolytics," Dr. Mason says.

"We would never question the cost of giving the thrombolytics," but she notes when hospitals are asked why they do not staff better, the answer is they cannot afford to hire more staff.

know what physicians are looking for and how they would prefer it to be presented.

A conversation with a friend showed Dr. Dickersin why some physicians get frustrated looking for answers in the Cochrane Library. Her friend, an ob/gyn, said she went to the Cochrane Library with a question; but when she did not find any evidence that addressed her question, she left and never went back. Surprised, Dr. Dickersin asked what the question was, and her friend's answer revealed a key issue in EBM searches. The clinician wanted to know what pregnancy would be like for a woman with multiple sclerosis. "That's a prognosis question," Dr. Dickersin says. "It's not even addressed by randomized trials, so no wonder it's not in the Cochrane Library, which really focuses on intervention."

Randomized, controlled trials (RCTs) are the best source of evidence for learning about what treatments and strategies work best, says Dr. Dickersin. "The trouble is, most of the literature in medicine is not randomized trials," so physicians get frustrated trying to find evidence that's not there. However, you don't always need an RCT. "If doctors understand that different types of designs answer different types of questions, maybe they will feel less frustrated," she says.

In the seminars that Dr. Dickersin teaches, she shows a diagram illustrating the hierarchy of evidence. "There's a lot of emphasis on the randomized clinical trial—and I'm a trials person myself; so I have been part of the problem—but I'm also anxious to try to fix the problem," she says. "Randomized trials are the best source of evidence for learning about what treatments work best, what prevention strategies work best, what diagnosis strategies work best—anything to do with an intervention. Should I take gingko to improve my quality of life? Should I take vitamin C to prevent a cold? Should I take aspirin to prevent a heart attack? Should I choose lumpectomy with radiation or mastectomy for breast cancer?"

"The hard part for doctors is [that] people are telling them randomized trials are the best evidence, but they don't see many out there for the questions they want answered. It ends up that doctors just throw up their hands and do what they've always been doing because they don't know how to deal with this problem,"

Dr. Dickersin says. "We were too pushy with our randomized trials without realizing that we'd skipped a step in our educational process."

"The trouble is," Dr. Dickersin goes on, "most of the literature in medicine is not randomized trials." Retrospective and case series studies make up most of the literature, she explains. As a result, she says, frustrated physicians may say, "There's no evidence for the question I'm asking" or "There's no randomized trial" that addresses their query. Instead, what they find are case series or retrospective studies in which physicians report on an interesting case they encountered or explore outcome trends within their own patient population.

Various kinds of evidence are useful when exploring different types of questions. "You don't always need a randomized trial," Dr. Dickersin says. For example, "If you're wondering what happens to children who are born with severe cerebral palsy over time—how long do they live—that's a prognosis question; and answering that by [citing results from] your last 100 patients, or preferably your last 25,000 patients, is the only way you can really address that question."

Randomized trials could tell the physician whether children with severe cerebral palsy who have trouble breathing do or do not fare better with a tracheotomy, because that's an intervention; but different study designs produce more applicable results when the question deals with prognosis or ideology, she explains. A prognosis question might be how long will a child with severe cerebral palsy live, or will a person with moderate cerebral palsy be able to hold a job. For a question such as what caused cerebral palsy in this child, an observational type of case-control study would be more appropriate than an experimental study. "If you're interested in the prevalence of this disease or how many cases of flu there were last year and how many beds we needed," Dr. Dickersin says, "those are all studies that are not done with a randomized trial."

"Our thought is that if doctors understand that different types of designs answer different types of questions, maybe they will feel less frustrated with the system they're in," Dr. Dickersin states. When physicians are frustrated by not finding the evidence they need, instead of "throwing up their hands," she says

"let's first go backwards and figure out what the questions are," then look for the best evidence for each of those questions.

She thinks the Cochrane Library is "as good as it gets" for evidence-based information, but it is only about interventions. UpToDate (*www.uptodate.com*) is more consensus based than evidence based, though she notes it is her understanding that the resource is moving more towards an evidence base. "UpToDate is about all different types of questions," she adds. "It is more the way doctors think. It's by and for doctors," but since it hasn't been evidence based, she advises physicians to weigh the evidence presented.

The key thing to remember is that "the hierarchy of evidence and level of evidence differ depending on the type of question you're asking," Dr. Dickersin says. If we approach EBM as one-solution-fits-all-problems, "we throw the baby out with the bath water," she adds.

Trans-disciplinary Approach

It will also help if we take a trans-disciplinary approach rather than "siloing" or teaching individual healthcare disciplines as separate entities, such as EBM, evidence-based nursing, evidence-based physical therapy, evidence-based psychiatry, says Bernadette Melnyk, Ph.D., R.N. Dr. Melnyk is co-editor of *Evidence-Based Practice in Nursing and Healthcare: A Guide to Best Practice* (Lippincott Williams & Wilkins, 2004). She is also Dean and Distinguished Foundation Professor in Nursing at the Center for the Advancement of Evidence-Based Practice (CAEP) at Arizona State University in Phoenix.

The trans-disciplinary approach works, Dr. Melnyk says, because "evidence-based practice is all the same process, whether you are a physician, a nurse practitioner, a physical therapist" or other healthcare provider. "Evidence-based practice is a problem-solving approach to the delivery of health care that integrates the best evidence from well-designed studies in combination with a clinician's expertise and a patient's preferences and values," she adds, noting, "It really sets people on a lifelong, very sound approach to clinical practice."

The CAEP Program at Arizona State University is based on five steps of evidence-based practice known as PICO(T), which

Dr. Melnyk explains this way: P stands for patient population. I is the intervention that physician is interested in, or if it's not an intervention, the treatment or area of interest. C is the comparison interval for the comparison group the physician is interested in, O is for the outcome, and T is for time (the time or duration of the study).

The first step is asking a clinical question in the PICO(T) format. The second step is searching for the best evidence. Dr. Melnyk says. "I think every healthcare provider should learn how to do this because we know that evidence has shown that patient outcome is at least 28 percent better when care is based on this approach to practice." (See sidebar "Evidence-based Practice Process.)

"When just the docs are at the table, you are missing a lot of other views—and not just from nurses," Dr. Mason explains. "You're missing psychologists, social workers, physical therapists, acupuncturists. If we are going to look at best practices, we need to bring in a group around the table that has different perspectives and who can look at the research not just from their own lens, but from a distance, more objectively."

But it's not just up to the physician. The environment has to be supportive of this approach in order to make the approach sustainable. Dr. Melnyk explains, "We can teach people the process; but unless there are supports in the environment where that person is practicing, to enhance their abilities to do this evidence-based practice, the chance of sustaining it is not real high."

Dr. Mason would take the process a step further. Best practices must be based on input from diverse sources, she says. "When you are talking about pain management and you have just the docs at the table, you are missing a lot of other views—and not just from nurses," she explains. "You're missing psychologists, social workers, physical therapists, acupuncturists. If we are going to look at best practices, we need to bring in a group around the table that has different perspectives and who can look at the research not just from their own lens, but from a distance, more objectively."

The first step, she says, it to look at well-done, systematic reviews of the literature. "Then," she says, "the question becomes: what if you don't have enough research? What do you

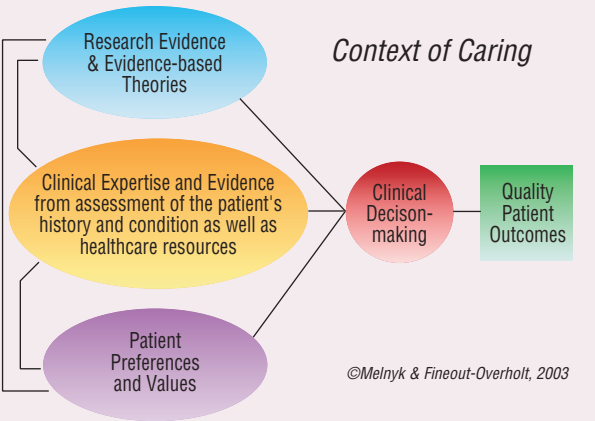
do?" She points to the example of the Women's Health Initiative findings on estrogen and heart disease in women. Although that study left many unanswered questions, women stopped taking

Evidence-based Practice Process

There are five steps in the process of Evidence-based Practice (EBP). Step 1 of EBP is asking a clinical question in PICO format (see below). As a first step, formulating the clinical question can be challenging, but is the most important part of the EBP process, laying the foundation for the 4 subsequent steps. A clinical question that is searchable and answerable creates the context for integrating research findings, clinical expertise and judgment, and patient values and preferences. It also provides direction for the search strategy and what type of evidence is required to answer it.

1. Ask the burning clinical question.
2. Collect the most relevant and best evidence.
3. Critically appraise and synthesize the evidence.
4. Integrate all evidence with one's clinical expertise, patient preferences, and values in making a practice decision or change.
5. Evaluate the practice decision or change.

The Merging of Science and Art: EBP within a Context of Caring Results in the Highest Quality of Patient Care



Source: http://nursing.asu.edu/caep/resources/process.htm

their medication as a result of it, whether theirs was the same drug as tested in the study or not. Was that the right decision? Was there enough information on which to base a decision? "That is a difficult question to answer," Dr. Mason says, but a clinician reading the research probably should not base his or her practice on just one study. "It requires a group of people to sit down and carefully and objectively filter through the literature and look critically at it before recommending a practice."

Assessing Applicability

"I think that it's very important for a physician to be aware of what the evidence is supporting their approaches," says D. Robert Dufour, M.D., Emeritus Professor of Pathology at George Washington University and the Veterans Administration Medical Center in Washington, D.C., and a member of the editorial board for Lab Tests Online (*www.labtestsonline.org*). He notes that physicians often don't pay as much attention as they should to the evidence that exists. Guidelines alone have not been an effective tool to change the way physicians practice medicine. "We need to focus more on ways to evaluate the strength of evidence," Dr. Dufour adds, "to help lead to changes in practice."

It can be very challenging to find evidence and figure out what information is solid, valid, and can or cannot be trusted, says Gwyn Barley, Ph.D., director for the Center for Advancing Professional Excellence at the University of Colorado School of Medicine. Her team works with medical students and residents as well as physician assistants and physical therapy students in various medical fields, asking questions such as how do you know this is a good study? How do you know you can trust these findings? Is this study applicable to the patient we just saw? Often the students will miss a key element of applicability, such as looking at a study that was done on men when the patient they're treating is a woman; but they learn they need to "dig deeper" and find a different study that fits the patient and answers the questions.

"We really push students to ground their questions and their research in the literature that's published," Dr. Barley says. "There are many different ways that we can gather new knowl-

edge and evidence, but it really is a learned skill that doesn't come to people intuitively."

For the physician who has been in practice for a few years or decades, Dr. Barley recommends taking a basic epidemiology course or one of the many research courses offered by medical libraries on how to read the literature. A basic course will suffice, she says. "You don't need a degree to do this, but you do need to spend time thinking about it and understanding what you look at in a study" and to master the terminology, which she says "is a language unto itself, but once you learn it and start using it, you don't forget it."

Keeping those skills sharp is vital to practicing EBM. Dr. Barley says physicians get into trouble "when they let their knowledge base deteriorate or atrophy. The biggest challenge of medicine is keeping up with it," she says. "It changes all the time; so anything you can do to [accomplish] that efficiently is extremely important in this day and age."

Learning how to manage and interpret information is the hardest thing about EBM, says Dr. Barley. It takes practice to develop a workable style or approach to dealing with the literature efficiently, but she notes this is much easier to do now than it was "even five or ten years ago because of the computer and the power that it brings in helping you get to things in a much more efficient way. It used to be that you ordered 20 journals, and they stacked up by your bed at night; and you were exhausted when you got home, and you fell asleep with a journal on your face. Now you don't have to do that anymore. You really can improve your quality of life and enjoy knowing as much as you need to know to take care of your patients."

With all the tools at the physician's disposal today, "There is no excuse for not practicing Evidence-based Medicine," Dr. Barley says. "Unless you are somewhere where you have no electricity, no Internet, no nothing—but even then you should still be thinking, 'I've got to know what's going on; I've got to have the latest information to take care of my population.'"

Detecting Bias

Although unbiased research is the ideal in medical science, the reality may fall short of that goal.

Studies published in the *Journal of the American Medical Association, Archives of Neurology, Archives of General Psychiatry, Archives of Dermatology,* and other journals have documented various forms of bias in published medical literature. It may manifest itself as selection bias, control group bias, context bias, exclusion bias, design-related bias, detection bias, indication bias, investigator or physician bias, publication bias, or other types.

Ideology is still another form of bias. Dr. Mason notes concern has been expressed about the extent to which ideology is driving policies and decisions such as those made by those made by the U.S. Food and Drug Administration, all of which should be based on science, she states. But, she adds, "There is also the concern of how good is the science?"

With all the tools at the physician's disposal today, "There is no excuse for not practicing Evidence-based Medicine," Dr. Barley says. "Unless you are somewhere where you have no electricity, no Internet, no nothing—but even then you should still be thinking, 'I've got to know what's going on; I've got to have the latest information to take care of my population.'"

Funding can also be a form of bias that may not be as readily noticed. Dr. Mason cites the recent 15-paper series on end-of-life care that was published by the *American Journal of Nursing.* As she and the series editors reviewed the papers, Dr. Mason noted that the studies focused only on drugs and asked the series editors why the studies didn't present other approaches to end-of-life care. One pointed out that all the studies happened to be drug focused because pharmaceutical companies fund much of the research.

Dr. Mason was concerned that the series was "inadequate" because it didn't address more approaches. To the uncritical or hasty reader, that body of published evidence may give the impression that drugs must offer the best approach because only drug studies were published. Dr. Mason would have preferred to see among the drug studies other approaches including non-drug therapies to provide a broader picture of what care options might be available and how well they might work. The pharmaceutical company-sponsored research was not flawed, and it did merit publication; but seeing the series as a unit made the absence of alternatives more notice-

able than it might have been otherwise. Other end-of-life care options may work less well, equally well, better, or not at all; but without funding to conduct studies on those other options alone and in comparison with the drugs, that evidence isn't available.

Another form of bias slants toward positive study results. Clifford Dacso, M.D., professor of medicine, chief of general medicine and vice-chair for clinical affairs in the Department of Medicine at Baylor College of Medicine in Houston, Texas, says, "It is very easy to get positive results published but difficult to get a negative clinical trial published," meaning one that did not show any improvement or difference as a result of the trial. "The journals don't want to publish that because it isn't 'sexy.'" But, Dr. Dacso says, "negative data is valuable, sometimes even more so than positive." He has heard of plans to start a journal devoted specifically to negative trials because that information is not getting out as it should.

"Negative and inconclusive studies do not sell papers" so they don't get reported by the popular media, either, Dr. Dacso says. However, he points out that "they are equally important because they tell you what you shouldn't be doing."

"Negative and inconclusive studies do not sell papers" so they don't get reported by the popular media, either, Dr. Dacso says. However, he points out that "they are equally important because they tell you what you *shouldn't* be doing." Although drug companies can't suppress the publication of a negative trial, they often don't support the publication, either. "So you get a real skew towards positive clinical trials; and as a consequence of that, you end up with these outlandish claims which are subject to the immutable law of statistics called regression to the mean. Whenever you see these wonderful studies, just wait."

If a study author discloses that he or she received a grant from the pharmaceutical company that makes the drug that the study investigated, it is important to know what that means, Dr. Mason says. Did it affect manuscript preparation? Did the author actually write the paper himself or herself? Or did someone else write the paper for the author? Did the pharmaceutical grantor send the author out on the speaking circuit to talk about the drug? Did a public relations firm influence how the paper was written?

Presenting a paper at a conference can also instill bias. Physicians in the conference audience assume the presented paper will be published and mentally accept it as valid. But not all papers presented at meetings hold up under peer review, Dr. Mason notes. She says her colleagues at *JAMA* have told her they've had papers whose conclusions were changed "to the total opposite of what they initially proposed" after peer review.

Presentation bias is the basis for the "Inglefinger Rule," Dr. Mason says. "Inglefinger was the editor of the *New England Journal of Medicine*. He decided if the researchers had already gone to the press with their findings, we [*NEJM*] won't publish it." That, she says, "is one of the reasons people should be very concerned about public media reporting of research results from conferences." (See box "The Inglefinger Rule.")

No Easy Answers

Using EBM doesn't mean that there are easy answers. In some areas, such as cancer screening, the application of EBM is still unclear, Dr. Luria says.

For example, he notes that prostate cancer screening is a controversial area and asks what, if anything, should be done to screen for prostate cancer. That may sound like a radical ques-

The Inglefinger Rule

Here is how the *New England Journal of Medicine* explains its own Editorial Policy on the *NEJM* Website:

"The *New England Journal of Medicine* has strict editorial policies governing the quality and originality of its content. These policies were established to protect the interests of our authors, readers and advertisers. Principal to our commitment is a policy known as the Ingelfinger Rule, which allows *NEJM* to consider a manuscript for publication only if its substance has not been submitted or reported elsewhere. This policy was promulgated in 1969 by the acting editor, Franz J. Ingelfinger and has been maintained by his successors.

NEJM editorial policies ensure advertisers that their message is contained within unique and timely medical research. Additional information and instructions are available in Information for Authors."

Source: http://nejmadsales.org/overview/editorialcontent.html#policies

tion; but Dr. Luria explains that for the past 15 to 20 years, PSA tests for prostate cancer have been advocated, and while "there are lots of stories that show" cases were detected at an early stage, it is not clear that early detection is always beneficial.

"There is no question we have caught lots more prostate cancers, and many of them are surviving much longer than the population we used to have," explains Dr. Luria. "Prostate cancer is a horrible disease, and it was the second most [common] cause of [cancer] death after lung cancer," he remembers, but it was not being detected until patients were symptomatic.

"Now we are finding folks who can go on for years and years" with prostate cancer, Dr. Luria says. But he cautions we have to ask, "Have we demonstrated that the wholesale screening for prostate cancer has truly impacted the death rate from prostate cancer?" Dr. Luria says. "Have we truly extended their lifespan? We still don't know that. Prospective studies are ongoing."

Some cases of prostate cancer are not very aggressive; yet patients may undergo aggressive treatments, such as surgery or radiation, that have significant morbidities—radiation enteritis, impotence, or erectile dysfunction. "It is not clear we have done these people any favors."

Dr. Luria says the evidence is less ambiguous for breast cancer screening, but there are still some murky areas. "The evidence is clear that after 50 a mammogram every year makes enormous sense," he says. "It's not so clear that it does before the age of 50, even though it is commonly done starting at the age of 40 or even earlier if it is in the family history. The problem is that breasts before 50 tend to be so dense with glandular tissue that, a) there are a lot of false positives, and b) a lot of things are missed."

Recommendations for Pap smears in young women are standard although, he notes, "that is very much a moving target, too" because of the HPV vaccine. He notes that the practices recommended by health agencies—such as the American Urological Association and American College of Gynecologists—may differ greatly from policies set by agencies such as the Canadian Task Force and the U.S. Preventive Services Task Force that "demand clear-cut evidence before they recommend a procedure."

The dearth of easy answers and the constant evolution of

information make it critical for physicians to take one more step in applying EBM in practice: to review the outcome and process to see what was beneficial, what could be improved, where weaknesses were in the system or in the physician's method, how useful the tools used by the physician were, what other tools might have been used instead or in addition, what steps might improve the process in the future, and what modifications need to be made to improve the physician's practice.

Constant updating must be part of the process, as Dr. Kramer says, because "Much of what you learn in terms of facts is going to be proven wrong in ten years." Everything becomes outdated; so reviews are essential to making EBM practice work.