

LETTERS AND COMMENTS

Transfer of Lamotrigine Into Breast Milk

TO THE EDITOR: Lamotrigine is an antiepileptic medication used in both bipolar disorder and epilepsy. As of June 28, 2006, there were reports of 12 women who had taken lamotrigine during lactation¹⁻⁴; these reports describe significant transfer of lamotrigine into milk (infant plasma concentrations ~30% of maternal) without adverse effects in the breast-fed infants. The aim of our study was to present additional data to assist physicians and patients in making informed risk-benefit assessments.

Methods. Six breast-feeding women (age 30–38 y) treated with lamotrigine at a mean dose of 400 mg/day (range 175–800) for epilepsy (n = 5) or bipolar disorder (n = 1) were recruited. They provided written informed consent under a protocol approved by 2 ethics committees. Their infants (breast-fed 50% for infant of Patient 1, 100% for others) were 2 girls and 4 boys, with a median age of 4.1 months (0.4–5.1) and a median weight of 5.6 kg (3–8) on the study day. The women collected milk samples by hand expression at various times (up to 14 times per pt.) over 1 or 2 dose intervals.

Infant health and well-being were investigated by interview of the mother and/or the referring physician, and body weight was assessed by reference to standard growth charts. Three infants were given a full clinical examination. Venous blood samples were collected from 5 of the mothers (1–6 samples per pt.) and their infants (1 sample per infant; Table 1). Lamotrigine concentrations in milk or plasma were measured by a validated HPLC method. Inter- and intraday relative standard deviations for the assay were less than 3.6%, with a limit of quantitation of 0.1 mg/L.

In 5 patients, AUCs were calculated for milk⁵ and average drug concentration in milk was calculated as $C_{avg} = (AUC)/\bar{U}$, where \bar{U} = dose interval. In one patient, milk C_{avg} was determined as the average of 4 measurements made on 2 days. Absolute infant dose (mg/kg/day) was calculated as the product of milk C_{avg} and an

infant milk intake of 0.15 L/kg/day.⁵ Relative infant dose (%) was calculated as absolute infant dose x 100/maternal dose (mg/kg/day). Infant plasma concentration (% of maternal plasma concentration) was calculated using data collected at the same time after dose.

Results. Study-day weight was unavailable for one infant. Infant body weights were within 50–95th percentiles, except for one (age 2 wk) who was between the 25th and 50th percentiles. No adverse effects were reported by the mothers or attending physicians. The clinical pediatric assessment performed for 3 of the infants also did not reveal any adverse findings. Table 1 summarizes maternal and infant doses and infant plasma concentrations as a percent of those in maternal plasma. Mean absolute infant doses, relative infant doses, and infant/maternal plasma lamotrigine values were 0.45 mg/kg/day, 7.6%, and 18%, respectively.

Discussion. The 4 previous reports of lamotrigine transfer into milk summarize data from 12 patients. The first details a single case of a mother taking 500 mg/day.¹ Absolute and relative infant doses and the infant's mean serum drug concentration (% maternal concentration) were 0.52 mg/kg/day, 13%, and 36%, respectively. The second is also a single case report (mother's dosage 250 mg/day) in which the absolute infant dose, relative infant dose, and infant plasma lamotrigine were 0.5 mg/kg/day, 10%, and 25%, respectively.² The third study, of 9 breast-feeding women (median dosage 300 mg/day), reported absolute infant dose, relative infant dose, and infant plasma lamotrigine values of 0.2–1 mg/kg/day, 9%, and 30%, respectively.³ The final study was a single case (maternal dosage 300 mg/day) in which the 4-month-old breast-fed infant's development was normal. No adverse effects were observed in these studies.

Our mean absolute infant dosage (0.45 mg/kg/day), relative infant dose (7.6%), and concentration of lamotrigine in the infant's plasma as percent of that in the mother's plasma (18%) were similar to those in previous reports. All infants in our study were observed at an age older than 12 days after birth and, given that lamotrigine's half-life is approximately 24 hours in neonates,⁶ drug exposure from pregnancy is unlikely to have influenced the infants' plasma concentrations. We also found no adverse effects in any of the infants. Hence, our study confirms and extends previously published data and brings the total of reported cases to 18. While this number is still small, the consistency of the data across studies, together with a lack of adverse events, are encouraging for the cautious use of lamotrigine when indicated. Use of lamotrigine during breast-feeding should always be subject to an individualized risk-benefit analysis. Regular observation of the infant's progress should be made, and occasional monitoring of plasma lamotrigine concentrations in infant and mother can be reassuring.

Table 1. Doses and Concentrations of Lamotrigine

Pt.	Maternal Dose, mg/kg/day	Absolute Infant Dose, mg/kg/day	Relative Infant Dose, %	Infant Plasma Concentration, mg/L ^a	Infant Plasma/Maternal Plasma, % ^b
1	4.71	0.42	8.9	0.9 (2.4)	13
2	8.81	0.75	8.5	0.3 (2.5)	3
3	7.16	0.53	7.4	ND	ND
4	1.75	0.1	5.7	0.5 (5.4)	33
5	12.5	0.67	5.4	0.6 (6)	ND
6	2.74	0.27	9.9	0.7 (17.7)	22
Mean	6.3	0.45	7.6	0.60	18
(95% CI)	(3.1 to 9.5)	(0.25 to 0.65)	(6.2 to 9.1)	(0.42 to 0.78)	(6 to 30)

ND = no plasma sample available for mother or infant.
^aFigures in parentheses are time of sample after mother's last dose (h).
^bMaternal concentrations not shown.

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Burning Mouth Syndrome Due to Efavirenz Therapy

TO THE EDITOR: Efavirenz, a nonnucleoside reverse transcriptase inhibitor, has mainly neuropsychiatric and cutaneous adverse effects. We report the case of a woman who developed burning mouth syndrome (BMS) related to the administration of efavirenz.

Case Report. A 42-year-old white woman who had been HIV-positive for 8 years presented to the Internal Medicine Outpatients' Clinic with symptoms of a BMS episode. She had no history of drug allergy. In 1997, she was started on antiretroviral therapy with stavudine, lamivudine, and saquinavir. Doses were in accordance with manufacturers' recommendations. The woman had responded appropriately to highly active antiretroviral therapy (HAART). In order to increase treatment adherence, saquinavir was replaced with efavirenz 600 mg once daily in October 2005. Two weeks after efavirenz was initiated, the patient reported constant, severe, oral burning symptoms including a burning sensation in the tongue, gums, and oral mucosa. She had no history of cigarette smoking or substance abuse and denied the use of any other drugs or herbal remedies. The oral cavity was normal, with no underlying medical causes such as lesions, erythema, or candidiasis. She had undergone no recent dental work and had no specific dental problems.

Results of a complete blood cell count, platelet count, glucose, serum electrolytes, creatinine, and liver function tests were within normal limits. The patient was not coinfecting with hepatitis B or C virus. A hormonal etiology was excluded because she was not postmenopausal. A diagnosis of BMS was made. The suspected causative agent was efavirenz, as this was the only drug that had been added to the long-standing regimen the patient was taking before the symptoms appeared. Efavirenz treatment was stopped and a new HAART regimen was started, including stavudine, lamivudine, fosamprenavir, and ritonavir. The BMS symptoms resolved within one week. No relapse was observed with the new HAART regimen and the patient remained asymptomatic.

Discussion. BMS is characterized by burning, stinging, heat, itching, or pain in the oral cavity and lips, usually in the absence of clinical and laboratory findings.¹ It affects women more frequently than men. Many local conditions such as infections, allergic reactions, and dental procedures have been proposed as causes; however, this condition is probably multifactorial in origin, and the etiopathogenesis of BMS remains unclear. Systemic causes of BMS include menopausal disorders, diabetes mellitus, and nutritional deficiencies. Psychological factors such as anxiety and depression have been consistently demonstrated in patients with BMS and have been used to suggest that the disorder is psychogenic.¹ The treatment of BMS is usually directed at its symptoms. Only 3 interventions have demonstrated a reduction in BMS symptoms: α -lipoic acid, clonazepam, and cognitive behavioral therapy.²

Case reports have linked BMS to the use of drugs.^{3,4} A MEDLINE search (1966–May 2006) was performed and we did not find any report of efavirenz as a cause of BMS. In our patient, there was a temporal relationship between the development of symptoms after starting efavirenz therapy. Other potential causes of BMS were ruled out. When efavirenz was discontinued, her symptoms improved and resolved quickly. Furthermore, efavirenz was the only drug added before the BMS symptoms appeared. In our patient, based on the Naranjo probability scale, efavirenz could be considered the probable cause of the BMS.⁵ To our knowledge, as of May 2006, this is the first report of BMS due to efavirenz therapy. This adverse reaction occurred while the patient was receiving the recommended efavirenz dosage and, although it is not life-threatening, BMS may be associated with significant poor treatment adherence and morbidity. Clinicians should be aware of this potential adverse effect of a widely used drug.

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Quetiapine in the Treatment of Tic Disorder

TO THE EDITOR: Current treatments for tic disorders such as Tourette's syndrome include haloperidol, clonidine, and pimozide, but adverse reactions limit use of these medications. Atypical antipsychotics such as risperidone, olanzapine, aripiprazole, and ziprasidone have been studied and found effective for Tourette's syndrome.^{1,2} As of June 13, 2006, no controlled studies of quetiapine in the treatment of this disorder exist. However, case reports and one open-label study have documented positive responses to quetiapine at doses of 50–400 mg/day.²⁻⁴ Our experience supports these findings and suggests that further investigation of quetiapine in tic disorders is warranted.

Case Report. A 26-year-old Hispanic male was admitted to a psychiatric crisis center. He displayed pressured speech, auditory hallucinations, paranoia, and erratic movements of the shoulders, head, and nose. The patient reported a previous diagnosis of bipolar II disorder and obsessive-compulsive disorder but was otherwise healthy with no substance abuse history. He stated that he had not taken any medications for 1 week. Prior to that time, he had taken valproic acid 500 mg/day, olanzapine 2.5 mg/day, and escitalopram (dose unknown). On admission, he was started on extended-release valproic acid 500 mg at bedtime, as well as quetiapine 50 mg twice daily and 25 mg every 4 hours as needed for agitation. Olanzapine was not reinitiated because of its adverse effect profile. On day 3 of treatment, the valproic acid dose was increased to 1250 mg at bedtime, based on a subtherapeutic concentration of 27 L (normal range 50–100), and the quetiapine dose was increased to 200 mg every morning and 400 mg at bedtime. The physician noted that his patient's anxiety had decreased, but involuntary movements, including blinking, shoulder shrugging, and a vocal tic, manifested as coughing/throat clearing became more evident. The patient was diagnosed with a tic disorder not otherwise specified. On day 6, both vocal and motor tics decreased significantly.

Discussion. Quetiapine has been described as a clozapine-like atypical antipsychotic because of its low affinity for dopamine D₂ receptors. Quetiapine is a weak antagonist of D₂, with a low incidence of adverse reactions like extrapyramidal symptoms, tardive dyskinesia, and endocrine symptoms. Dopamine antagonism is thought to play a role in the treatment of tics. The mechanism of action of quetiapine in the treatment of tic disorders cannot be fully explained by dopamine antagonism. The blockade of receptor subtypes such as the D₄ and/or serotonin (5-HT₆)

receptor⁵ or selective inactivation of mesolimbic cortical dopamine neurons producing an alteration in the expression of excitatory amino acids³ may explain quetiapine's benefit in Tourette's syndrome.

Limitations to our observations include the loss of the patient to follow-up, concurrent use of valproic acid, waxing and waning of the tic disorder, and subjective reports of improvement. Valproic acid is not used in the treatment of tics, and the mechanism of action is generally unknown. However, it may attenuate the inhibitory neurotransmitter γ -aminobutyric acid and subsequently inhibit dopamine. When combined with quetiapine, this action may enhance the inhibition of tics. The use of quetiapine in the management of tic disorders is controversial but may have the advantage of a lower incidence of adverse reactions, compared with traditional dopamine antagonists used in tic disorders.

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Potential Drug-Food Interactions with Pomegranate Juice

TO THE EDITOR: Pharmacokinetic studies have implicated pomegranate juice as having human cytochrome CYP450 enzyme inhibitory activity similar to that of grapefruit juice, thereby prompting a concern for potential drug-food interactions.

The pomegranate (*Punica granatum*) is an edible fruit historically complementing diets and complementary medicine practices in Mediterranean and Eastern cultures. In the US, the pomegranate fruit and its juice have recently become increasingly popular, fueled in part by the

touting of its health benefits by the lay press.¹ Pomegranates are rich in polyphenolic compounds and have been shown to have more antioxidant activity than either red wine or green tea.² In vivo studies have been performed to ascertain the potential clinical benefits of pomegranates. For example, pomegranate juice extract fed to rats implanted with prostate cancer cells inhibited tumor growth and decreased secretion of prostate-specific antigen.² In another study, humans ingesting pomegranate juice for 3 months had less inducible ischemia as measured by myocardial perfusion scans compared with control subjects ($p < 0.05$).³

Despite promising evidence of clinical benefit, recent pharmacokinetic studies indicate that pomegranate juice inhibits CYP3A enzyme activity. In an in vitro study examining the extent to which tropical fruits inhibit the midazolam 1'-hydroxylase activity of CYP3A, incubation with pomegranate juice led to 3.2% residual enzyme activity compared with control. In comparison, grapefruit juice resulted in 14.7% residual activity.⁴ In another pharmacokinetic study, Hidaka et al.⁵ showed that incubation of pomegranate juice (5% v/v) with human liver microsomes resulted in 1.8% residual CYP3A activity for converting carbamazepine to carbamazepine 10,11-epoxide. Further analyses revealed the inhibitory activity of pomegranate juice to be dose-dependent. Residual CYP3A activity 30 minutes after preincubation with pomegranate juice was 45.7%; in comparison, residual activity following grapefruit juice preincubation was 38.3%. In addition, both the maximum concentration and AUC of carbamazepine in rats given pomegranate juice were significantly higher than those in the control group ($p < 0.05$) and were comparable with values achieved in rats given grapefruit juice. Additional testing suggested that recovery of CYP3A activity occurs within 72 hours following removal of pomegranate juice ingestion. Although these 2 pharmacokinetic studies indicate that pomegranate juice has inhibitory activity comparable to that of grapefruit juice, a more recent in vitro study measuring CYP3A-catalyzed midazolam 1'-hydroxylation showed that grapefruit juice had greater inhibitory potency than pomegranate juice.⁶

Studies of pomegranate juice do have limitations. Since the effect of pomegranate juice on drug metabolism of rats may differ from that of humans, pharmacokinetic studies in human subjects must be performed before pharmacists make recommendations regarding concomitant use of pomegranate juice and CYP3A substrates. Also, no clinically relevant interactions involving pomegranate juice and drugs metabolized by CYP3A have yet been reported. However, at this time, pharmacists should consider the evidence that pomegranate juice may have CYP3A inhibitory activity comparable to that of grapefruit juice. When evaluating the available evidence implicating pomegranate juice as a CYP3A inhibitor, pharmacists should also note that the strong inhibitory activity of grapefruit juice initially seen in in vitro studies was eventually validated clinically through observations of rhabdomyolysis induced by concomitant administration of grapefruit juice and simvastatin.^{7,8} Accordingly, as the media exposure of pomegranates as a healthy "super food" continues to increase,¹ pharmacists may begin encountering more patients with potential drug-food interactions.

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Comment: Frequency of Serum Creatinine Monitoring During Allopurinol Therapy in Ambulatory Patients

TO THE EDITOR: We read with interest the recent retrospective cohort study by Raebel et al.¹ concerning the frequency of renal function monitoring in ambulatory patients with gout receiving allopurinol. Raebel and colleagues found that approximately 25% of patients who received allopurinol and had a diagnosis of gout (based on data from 10 US health maintenance organizations) did not have serum creatinine monitoring over a one year period. They concluded that these patients were at increased risk for serious adverse effects from allopurinol use if declining renal function went unnoticed and the allopurinol dosage was not adjusted. We are concerned that the basis for this assertion is not fully supported by the peer-reviewed literature.

The most feared toxicity from allopurinol is the so-called allopurinol hypersensitivity syndrome (AHS). This rare syndrome, with symptoms including exfoliative dermatitis, liver or renal dysfunction, and eosinophilia, is fatal in up to 20% of cases.² The mechanism of AHS is unknown but is thought to be immunologic in origin. Many immunologic toxicities are considered idiopathic rather than dose-related, yet the possible association with increasing concentrations of allopurinol's primary metabolite oxypurinol led Hande et al.,³ to recommend reducing the allopurinol dose in patients with renal failure. In this retrospective review of 78 patients (6 of their own patients, 72 cases reported in the literature) with AHS, 81% had significant renal insufficiency and were started on standard doses of allopurinol. Symptoms of AHS occurred within 3 weeks in nearly all patients. Hande et al.'s report suggested an association (not causation) of higher doses of allopurinol and the development of AHS.

This report was challenged by another retrospective study of 120 patients with gout, 44% of whom had an estimated creatinine clearance of less than 50 mL/min.⁴ These investigators compared patients who received a reduced dosage concordant with this degree of renal insufficiency with patients whose dosage was not reduced and found no significant increase in any adverse effects in the latter group. Indeed, the only patient in the study who developed AHS had normal renal function and had received a standard dosage of allopurinol.

The matter of dose is important, because the ability of allopurinol to lower serum uric acid level is dose-related. Some have suggested that a

Comments on articles previously published are submitted to the authors of those articles. When no reply is published, either the author chose not to respond or did not do so in a timely fashion. Comments and replies are not peer reviewed.—ED.

major reason for clinical failure of allopurinol is underdosing. A lack of familiarity with previous studies regarding allopurinol dosing issues may be a reason for this underdosing. We are certainly not suggesting that monitoring serum creatinine is unimportant in patients with gout who are taking allopurinol. The possibility of uric acid nephropathy is reason enough to warrant such monitoring. However, we agree with the quality of care guidelines that the initial dose of allopurinol should be adjusted according to the patient's baseline renal function.⁵ If dose increases are required to achieve a target serum uric acid level, this should be done and the patient should be monitored closely over at least 30 days.

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AUTHORS' REPLY: We thank Drs. Wall and Krypel for their interest in our article. We wish to point out that the interpretation they give to the conclusion of our article is not entirely aligned with what we stated. We stated that lack of serum creatinine evaluation and of allopurinol dosage adjustment when indicated could potentially increase the risk of drug toxicity.

We are familiar with the controversy cited by Wall and Krypel relative to therapeutic failure, and we agree that lack of allopurinol effectiveness can be related to inadequate drug dosing. However, we also believe that factors associated with serious allopurinol toxicity are only partially understood, and it is therefore appropriate to weigh the risks and benefits of various allopurinol dosages (ie, <300 mg/day, 300 mg/day, >300 mg/day) along with the clinical situation of the patient (eg, the severity of gout and of renal insufficiency) to individualize allopurinol dosing for each patient. Within this framework, the fact that one-fourth of patients prescribed allopurinol do not have serum creatinine monitoring performed within a 1 year period is concerning.

We reiterate the statement in the conclusion of our article that evidence must be developed to determine whether excess morbidity is associated with failure to monitor serum creatinine and/or whether patient outcomes differ between patients receiving allopurinol who have serum creatinine monitoring performed and those who do not. This would in-

clude both therapeutic effectiveness outcomes and adverse event outcomes.

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Comment: Pharmacist Critique was Ill-Informed

TO THE EDITOR: The opinion expressed by Dr. Karpa¹ in this issue of *The Annals* is a thorough and eloquent rebuttal to the commentary by Wall and Brown in *Obstetrics and Gynecology*.² I completely agree with her comments. When I read the Wall and Brown article, one of my first thoughts was that their knowledge of our profession extends only to retail pharmacy; in other words, they have little or no contact with clinical pharmacists. I found this to be very strange in light of the advancements made by our profession over the past 30+ years. Then it occurred to me that our profession may be partially to blame. Perhaps there are more, but I am aware of only 4 programs in which clinical pharmacists provide full-time services to obstetric/gynecologic patients. Even worse, with one exception, I am not aware of any pharmacy school curriculum that includes any mention of reproductive toxicology or the unique pharmacology, drug therapy, or diseases/complications associated with pregnancy. There are many pharmacists involved in women's health, but this does not mean that they have an in-depth understanding of these topics; nor does it indicate whether their practice primarily involves obstetric patients.

I have been working almost exclusively with obstetricians/gynecologists and their patients for more than 20 years. Three years ago, a second pharmacist joined my practice and our group will expand to 4 in July. We attend daily patient care rounds, participate as principal or coinvestigators in clinical research, and are voting members of medical staff committees. The clinical services that we provide include drug therapy management of diseases in pregnant and nonpregnant women (both inpatient and outpatient); drug information for physicians, nurses, and patients; and development of "best practice" drug therapy guidelines for obstetric and/or gynecologic patients. As clinical faculty for 2 schools of pharmacy, we teach an elective, 6 week obstetric/gynecologic clerkship and help train clinical pharmacy residents rotating through our area. We frequently deliver lectures to medical students, obstetric/gynecologic and family medicine residents and fellows, and attending physicians. Perhaps if

these services had been available at Washington University, Wall would never have coauthored the article.

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Comment: Pharmacist Critique was Ill-Informed

TO THE EDITOR: I read with great interest and disappointment the commentary by Wall and Brown,¹ entitled "Refusals by Pharmacists to Dispense Emergency Contraception," that appeared in the May 2006 issue of *Obstetrics and Gynecology*. In this editorial, the authors begin their assault on the pharmacy profession by citing a true story of a pharmacist who refused to fill a prescription for an oral contraceptive that was prescribed for a 14-year-old girl with anovulatory uterine bleeding. The pharmacist was under the misguided assumption that the drug was an abortifacient and proceeded to berate the patient and her mother. Although I cannot condone such behavior, this kind of occurrence is most certainly the exception rather than the rule regarding pharmacists' professional conduct.

In a June 23, 2005, press release,² John A Gans PharmD, executive vice president and chief operating officer of the American Pharmacists Association, reiterated the association's position that "patients should receive their medications without harassment and interference." However, the association also maintains that pharmacists have the right to refuse to fill a prescription based on moral and ethical grounds. Importantly, patient care must not be compromised as a result of such action, and drug delivery systems must be in place to guarantee that patient abandonment (real or perceived) is never realized. It is important to note that physicians and nurses have been operating under conscience clauses in their respective practice acts for many years, thus allowing them to withdraw from participation in professional activities deemed to be morally or ethically objectionable.³⁻⁵ The American Medical Association's House of Delegates recently adopted 9 "Principles of Medical Ethics" to guide physician conduct and behavior.⁶ The following principle attests to a physician's freedom of choice: "A physician shall, in the provision of appropriate patient care, except in emergencies, be free to choose whom to serve, with whom to associate, and the environment in which to provide medical care." Although this principle is not legally binding, it appears to legitimize a physician's decision to refuse treatment deemed personally unacceptable.

Wall and Brown use the above mentioned factual example and a hypothetical case to question the right of pharmacists to refuse to fill prescriptions based on personal and ethical grounds. Upon closer scrutiny, the article appears more like a lesson in medical terminology, reproductive physiology, and emergency contraception. Particularly troubling is their portrayal of pharmacists as nothing more than unethical technicians, inept communicators or, at best, "incomplete" quasiprofessionals who put political agendas before patient care. The misguided notions that the patient represents a pharmacist's customer, with no expectation of a professional encounter, and that the pharmacist should merely carry out a physician's orders, without independent thought, judgment, or action, reinforces my opinion that the authors are woefully misinformed

about contemporary pharmacy practice. I am convinced that Wall and Brown are unaware of the paradigm shift to the pharmaceutical care model that occurred 15 years ago, the implementation of collaborative practice initiatives between pharmacists and physicians, the growth of consultant and senior care pharmacy practice, and the opportunities afforded pharmacists under the new Medicare Part D guidelines for providing expanded patient care services.⁷ Wall and Brown would be well advised to examine 2 recent publications that provide a perspective on contemporary pharmacy education and postgraduate training programs that prepare pharmacists to provide a sophisticated level of pharmacotherapy for selected patient populations.^{8,9}

The authors' sweeping generalizations and assumptions about the professional conduct of pharmacists are grossly unfair, represent conjecture at best, and attest to their inattention to adequately researching the subject matter prior to sharing their opinions with the medical community at large. In fact, all one has to do is review the authors' reference list to see that they did not do their "homework." There is only one reference (of 14) that mentions the pharmacy profession (eg, in reference to incomplete professionalization) and it is nearly 40 years old!¹⁰

Despite their myopic view of the profession, Wall and Brown confront the reader with unavoidable realities regarding shortcomings that the profession still faces. The following quote from the article is particularly thought provoking and rings true today: pharmacists "do not exercise full autonomous control and authority over their area of expertise." We have struggled for many decades to shed that perception of ourselves as being just glorified technicians—those who merely "lick and stick" and "count and pour." Historically, we have succeeded at intraprofessional communication (pharmacist to pharmacist, organization to organization), but we still struggle with articulating our role and value to other healthcare providers, third party payers, and most importantly, the public. For example, the Public Policy Institute of California conducted a statewide survey in 2005 to assess public opinion of the state's population.¹¹ Germane to this discussion, only 18% of respondents knew that emergency contraception was available from a pharmacist without a prescription. Whereas the reason(s) for this lack of awareness are unknown, one must wonder whether the blame lies, in part, with the pharmacy profession itself.

Nonetheless, during the past 10 years, the expanding roles of the pharmacist in medication management and collaborative practice, as well as the beneficial clinical, economic, and humanistic outcomes ascribed to these services, have been articulated in the literature.^{12,13} These well known success stories have validated the role of the pharmacist as the rightful provider of pharmacotherapy and have provided the fabric with which to cloak the pharmacist with the mantle of complete professional.

The authors are correct in implying that pharmacists neither fully function as professionals nor make appropriate decisions when critical elements of the medical record are inaccessible to them. This only reinforces the need to collaborate with physicians, other healthcare providers, and informatics experts in developing an infrastructure that would facilitate access to a shared electronic medical record. The electronic medical record can serve as a link among interdisciplinary providers and the patient to facilitate care coordination, eliminate redundancy, streamline care, and optimize clinical, socioeconomic, and humanistic outcomes.¹⁴ Simply persuading physicians to consistently write the diagnosis on a prescription would go a long way toward solving this problem. It is certainly true that we have come a long way, but, as we have seen from this article and the perceptions of its authors, we still have a long way to go.

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Comment: Increased Sensitivity to Warfarin after Heart Valve Replacement

TO THE EDITOR: In their recent article in *The Annals*, Rahman et al.¹ concluded that, after cardiac valve replacement, patients are more sensitive to warfarin and should receive a lower dose during the initial phase of treatment. In that study, all patients received 5 mg of warfarin for the first 2 days following surgery. A regimen using 2.5 mg of warfarin for the first 2 days after surgery in such patients has been suggested; this regimen has been shown to cause a reduced incidence of elevated international normalized ratio (INR) during initiation.² Rahman et al. noted that “during initiation of oral anticoagulation following heart valve replacement, patients have a tendency to exceed the upper limit of the targeted INR range despite regular monitoring,” and reported that 25% of their patients had an INR higher than 4 during initiation.

To demonstrate that a reduced initiation dosage of warfarin could be beneficial in this setting, we conducted a comparison of results from Rahman et al.'s investigation with those from similar patients initiated on warfarin at the Royal Hobart Hospital (RHH), Tasmania, Australia, following heart valve surgery (Table 1). This was part of an ongoing study of warfarin initiation at RHH. An initiation dose of 3 mg was given for

the first 2 days and then adjusted according to the INR to allow for pacing wire removal at an INR lower than 1.6; the dose was then adjusted to achieve a therapeutic INR prior to discharge. The 3 mg regimen used at the RHH resulted in a much lower incidence of INRs greater than 4 during initiation, which is a commonly cited indicator of excessive anticoagulation during initiation. Importantly, Rahman et al. excluded patients who received drugs that are known to interact with warfarin to enable them to better study warfarin sensitivity; in our cohort, all patients received prophylactic doses of intravenous cefazolin following surgery. Additionally, significant numbers of patients received amiodarone and oral antibiotics during the initiation of warfarin; these drugs are known to elevate the INR.³

Despite the presence of these interacting medications, a much lower incidence of elevated INRs was demonstrated in our cohort. Indeed, for elderly patients in general, there is a growing body of evidence to suggest that initiation doses of warfarin of less than 5 mg/day may be beneficial.^{4,5} It is likely that overaggressive initial dosing of warfarin in the elderly population is at least partly responsible for the higher rates of bleeding that have been reported in the early phase of treatment. It is logical to assume that improving the quality of warfarin initiation in cardiothoracic patients will reduce the rate of major bleeding and improve patient outcomes. Despite the demonstrated sensitivity to warfarin after heart valve surgery, it may be possible to achieve lower rates of excessive anticoagulation during initiation, even in the presence of interacting drugs and advanced age, by using a 3 mg rather than a 5 mg dose for the first 2 days of therapy.

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Table 1. Comparison of Two Cohorts of Cardiothoracic Patients Initiated on Warfarin^a

Characteristic	Rahman et al. ¹	RHH
Pts., N	111	127
Mean age, y	65.39 ± 10.55	64.29 ± 12.42
Men, n (%)	66 (59.5)	84 (66.1)
Mean day 1 dose, mg	5.0	3.0 ± 0.5
Mean day 2 dose, mg	5.0	3.0 ± 0.6
Target INR range, n (%)		
2.0–3.0	NR	38 (29.9)
2.5–3.5	NR	89 (70.1)
Concomitant interacting medications, n (%)		
amiodarone	0 (0.0)	40 (31.5)
antibiotics	0 (0.0)	56 (44.1)
Median stay, days (range)	9 (7–15)	9 (4–65)
INR >4 during initiation, n (%)	28 (25.2)	6 (4.7)

INR = international normalized ratio; NR = not reported; RHH = Royal Hobart Hospital
^aMean ± SD.

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Correction: Résumé—Argatroban Dosing of Patients with Heparin-Induced Thrombocytopenia and an Elevated aPTT Due to Antiphospholipid Antibody Syndrome

In this case report, published in the May 2006 issue (2006;40:972-6), the résumé was not complete. The complete résumé follows:

OBJECTIF: La thrombopénie induite par l'héparine (TIH) avec ou sans manifestation thromboembolique est une complication dévastatrice de l'exposition à l'héparine. Les recommandations sont d'arrêter toutes les formes d'héparine et de mettre en œuvre immédiatement un autre traitement anticoagulant. Les 2 seuls médicaments approuvés par la FDA

pour le traitement des TIH avec ou sans manifestation thromboembolique sont 2 inhibiteurs directs de la thrombine (IDT): l'argatroban et la lépirudine. Tous 2 nécessitent un suivi du temps de thromboplastine partielle activée (TTPA). La surveillance du TTPA chez des patients avec un TTPA de base anormal dû à un syndrome des antiphospholipides (SAPL) n'est pas fiable. L'objectif de la série de cas présentés est de décrire les caractéristiques cliniques, la prise en charge et les résultats des patients avec une TIH avec ou sans manifestation thromboembolique qui présentaient aussi un TTPA de base augmenté dû à un SAPL.

RÉSUMÉ DU CAS: Quatre patients avec une TIH et un TTPA de base augmenté dû à un SAPL ont été identifiés. Deux patients présentaient une thrombose veineuse, 1 une ischémie d'un membre et 1 une TIH isolée. Tous 4 ont reçu de l'argatroban sans suivi biologique. Aucun de ces patients n'a présenté de complications thrombotiques ou hémorragiques une fois le traitement débuté.

DISCUSSION: La prise en charge des patients avec une TIH avec ou sans manifestation thromboembolique et un TTPA de base augmenté dû à un SAPL est problématique. Les auteurs font le point sur les résultats favorables des 4 patients traités par argatroban sans suivi biologique. Ils font aussi le point sur les autres stratégies de prise en charge, telles que le suivi d'un traitement par IDT au moyen du temps d'écarine ou du temps d'inhibition de la thrombine, ou l'emploi d'autres anticoagulants comme le fondaparinux. A l'heure actuelle, aucune de ces stratégies thérapeutiques n'a été évaluée dans un essai clinique chez cette population de patients.

CONCLUSIONS: Les auteurs estiment que l'emploi d'argatroban sans suivi biologique est une stratégie thérapeutique envisageable pour des patients présentant une TIH et un TTPA de base augmenté dû à un SAPL.

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Letters are subject to review prior to acceptance. They should address areas related to pharmacy practice, research, or education, or articles recently published. Corrections of previously published material also are accepted. Letters are limited to no more than five authors. In cases where adverse drug effects are described, the Naranjo ADR probability scale should be used to determine the likelihood that the adverse effect was drug-related (*Clin Pharmacol Ther* 1981;30:239-45). Text: limit 500 words. References: limit 5. Art: limit 1 table or figure.