

Protecting Patients from Adverse Drug Events: Propoxyphene, PIMs, and Drugs to Avoid in Older Adults

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The base of evidence for the relative harm versus benefit for commonly used prescription drugs expanded in 2010, including developments late in 2010 that reinforced the value of pharmacovigilance and the need for critical appraisal of warnings of threat to patient safety. In October 2010, the U.S. Food and Drug Administration (FDA) announced additions to the labels of all bisphosphonates warning of the increased risk of atypical fracture of the femur, an outcome that although rare (representing less than 1% of all fractures of the hip and femur) had been “predominantly reported in patients taking bisphosphonates.”¹ These drugs already carried a label warning regarding osteonecrosis of the jaw, and the additional warning precipitated widespread discussion among patients and health care professionals regarding the safety of bisphosphonates and the observation that these widely used drugs were associated with adverse events that they were intended to prevent.² In September 2010, a 4-year controversy over the relative benefit versus harm of rosiglitazone culminated in withdrawal of the drug from the European market and exceptionally restricted use in the United States including the requirement that patients “acknowledge they understand the [cardiovascular] risks” associated with use of rosiglitazone.³ The clinical irony for rosiglitazone is that it was used by millions of people with type 2 diabetes to prevent the very adverse cardiovascular events that were found to be associated with its use.^{4,5} It is not yet clear how much of the cardiovascular adverse event profile pioglitazone shares with rosiglitazone,⁶ and pioglitazone has a black-box warning regarding the possibility to “cause or exacerbate congestive heart failure.”⁷

New Evidence About Relative Harm of Opioids, NSAIDs and COX-2 Drugs in Older Adults

In December 2010, Solomon et al. reported the finding that opioids pose a higher risk of harm than nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors among elderly patients with arthritis.⁸ This observational analysis of pharmacy and medical claims data for 12,840 low-income Medicare beneficiaries enrolled in pharmaceutical assistance programs in 2 states (New Jersey and Pennsylvania) over the 7-year period from January 1, 1999, through December 31, 2005, used extensive propensity score matching in an attempt to remove the effects of confounders, and the analysis was limited to new users of prescribed analgesics in an effort to increase comparability among groups. The

scope of outcome measures was also impressive, with assessment of 15 well-documented and transparently reported individual safety events (e.g., myocardial infarction, stroke, upper gastrointestinal bleed, falls, and 4 fracture types), grouped into 6 composite outcome measures. An important limitation of the study was that data on over-the-counter (OTC) use of nonselective NSAIDs were not available; thus, it is possible that the incident users of prescribed medications had previously used OTC NSAIDs or that opioid users were taking OTC NSAIDs concomitantly.

Compared with nonselective NSAIDs, composite cardiovascular events (including fatal and nonfatal myocardial infarction and 4 other individual outcomes) were more common with COX-2 inhibitors (hazard ratio [HR]=1.28, 95% confidence interval [CI]=1.01-1.62) and opioids (HR=1.77, 95% CI=1.39-2.24) in this sample of older adults (mean age 80.0 years; approximately 85% female). Risk of the second composite outcome, gastrointestinal bleeding, was lower for COX-2 inhibitors compared with nonselective NSAIDs (HR=0.60, 95% CI=0.35-1.00) but similar for nonselective NSAIDs and opioids. The composite outcome of fracture risk (hip, pelvis, wrist, and humerus) was higher for opioids compared with nonselective NSAIDs (HR=4.47, 95% CI=3.12-6.41) but similar between nonselective NSAIDs and COX-2 inhibitors; and the composite outcome for all-cause mortality was higher for opioids compared with nonselective NSAIDs (HR=1.87, 95% CI=1.39-2.53) but similar for COX-2 drugs and nonselective NSAIDs. There was no significant difference among the 3 classes of drugs for death related to an adverse event, but the absolute counts were small (68 events in the sample overall, incidence rates of 12 to 13 events per 1,000 person years). Adverse events that required hospitalization were the most common safety event, and opioids but not COX-2 inhibitors were associated with increased risk of harm compared with nonselective NSAIDs (HR=1.68, 95% CI=1.37-2.07); the absolute rates per 1,000 person years were 100 for COX-2 inhibitors, 105 for NSAIDs, and 155 for opioids.

The class of opioids in the study reported by Solomon et al. included propoxyphene, but the adverse events were not reported for specific drugs.⁸ However, in a coincident report, these researchers found differences in safety among specific opioid products.⁹ Like the report on safety of analgesics overall, the opioid-specific study used propensity score matching in an attempt to reduce the effects of confounders in a cohort

analysis of pharmacy and medical claims. The opioid-specific study examined dates of service from January 1, 1996, through December 31, 2005, for 31,375 Medicare beneficiaries in 2 states (New Jersey and Pennsylvania) who qualified for pharmaceutical assistance programs and were new users of opioid therapy for nonmalignant pain (i.e., cases with a cancer diagnosis or use of hospice care were excluded).

Over the 10-year study period, propoxyphene and tramadol were associated with a lower risk of fracture compared with hydrocodone (rate ratio [RR]=0.54, 95% CI=0.44-0.66; and RR=0.21, 95% CI=0.16-0.28, respectively). Among the 5 types of opioid therapy (hydrocodone, oxycodone, codeine, propoxyphene, and tramadol), the risk of cardiovascular events was significantly higher for codeine during the first 180 days after initiation of therapy (RR=1.62, 95% CI=1.27-2.06) but not during the first 30 days, and there was no significant difference in the risk of gastrointestinal events in either time period. Compared with hydrocodone, oxycodone and codeine were associated with increased risk of all-cause mortality during the first 30 days of therapy (RR=2.43, 95% CI=1.47-4.00; and RR=2.05, 95% CI=1.22-3.45, respectively). Becker and O'Connor posited separately in a commentary that the lower potency of tramadol and propoxyphene may explain the lower risk of fracture compared with the more potent opioids hydrocodone and oxycodone.¹⁰

Public Health Implications of Evidence About Analgesic Safety in Older Adults

The report by Solomon et al. of greater harm in older adults associated with opioids compared with NSAIDs and COX-2 drugs followed action by the FDA intended to better manage the safety of opioid use. In July 2010, a joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee advised the FDA that its proposed risk evaluation and mitigation strategy (REMS) for extended-release and long-acting opioid drugs did not go far enough because the misuse of both immediate-release and extended-release opioids “has a huge impact on public health,” indicating a need for REMS for both opioid categories and “a concerted public health campaign” involving “prescribers, pharmacies, patients, and industry.”¹¹

Nearly 9 years after the Department of Health and Human Services (DHHS) called for a “national action plan” to ensure the appropriate use of therapeutic agents among older adults,¹² the nagging question is, are we making progress? The 2 studies by Solomon et al. raise an important issue with potential implications both for public health and for provider education campaigns—whether clinicians are running from the fear of gastrointestinal toxicity and nephrotoxicity associated with nonselective NSAIDs and cardiovascular toxicity of COX-2 drugs toward potentially more dangerous opioids, resulting in avoidable harm to older adults.

In commenting on the work of Solomon et al., Graf suggests that clinicians need to pay attention to these findings indicating that nonselective NSAIDs may be safer than either opioids or COX-2 drugs in the care of older adults with the common condition of arthritis because analgesic use is becoming an increasingly important public health issue.¹³ Graf argues that several factors—public perceptions about inadequate pain control, insufficient provider attention to diagnosing and treating the underlying causes of pain, institutional pain assessment protocols, and even legislation specifying patient “rights” to opioids—have contributed to increased use of opioids, especially among females aged 65 years or older with chronic non-cancerous pain. Supporting Graf’s assertion of the need for provider attention to the problem, Solomon et al. concluded that opioid use for nonmalignant pain in older adults is a clinical concern, based in part on the calculation of the number needed to harm during the first 365 days of therapy: only 27 patients would need to be treated with an opioid or 66 patients with a COX-2 inhibitor instead of a nonselective NSAID to result in 1 excess all-cause death.⁸

With a Stroke of the Pen in November 2010, Are Older Adults Safer?

The FDA announced on November 19, 2010, that it had obtained agreement from the manufacturer of brand propoxyphene products (Darvon and Darvocet) to withdraw these drugs from the U.S. market and that it was working with the generic manufacturers to voluntarily withdraw all propoxyphene-containing products.¹⁴ The FDA cited new safety data submitted by the manufacturer that confirmed previous data indicating an increased risk of potentially fatal cardiac arrhythmia associated with propoxyphene, advising health care professionals to stop prescribing propoxyphene and patients to contact their prescribers to obtain alternative therapy. Data from SDI/Verispan (SDI Health, Plymouth Meeting, PA) showed that there were 17.5 million prescriptions dispensed for propoxyphene brand and generic products in 2009, making it the 38th most prescribed generic drug in the United States in 2009.¹⁵

The decision by the FDA in November 2010 to withdraw propoxyphene from the U.S. market was neither sudden nor unexpected. Propoxyphene was banned from the United Kingdom (U.K.) in 2005 and from the European Union in 2009.¹⁵ An FDA advisory committee voted 14-to-12 in January 2009 to recommend U.S. market withdrawal of propoxyphene, and the FDA asked the manufacturer for additional safety data;¹⁴ a black-box warning was added to the propoxyphene label in September 2009 regarding increased risk of death from overdose.¹⁶

Interestingly, the observational research reported by Solomon et al. in December 2010 did *not* provide convincing support for the FDA’s decision the previous month to remove propoxyphene from the U.S. market. Specifically, in

TABLE 1 Historical Events in Development of Measures of Potentially Inappropriate Prescribing in Older Adults^a

Measure	Target Population	Number of Drugs and Changes to Previous Measure
Beers, 1991 ⁴⁹	Older adults in nursing homes	Expert consensus panel of 13 members developed 30 criteria, identifying 19 individual drugs or classes to avoid.
Beers, 1997 ²⁸	Older adults in the community	Expert consensus panel of 6 members identified 28 drugs or classes to avoid independent of diagnoses and 35 drugs or classes to avoid with any of 15 known medical conditions.
Zhan-AHRQ, 2001 ²⁷	Older adults in the community	Expert panel of 7 members classified 33 drugs from the 1997 Beers list into 3 categories irrespective of dose, frequency of administration, or duration: (a) Always Avoid (11 drugs, including dicyclomine, chlorpropramide, flurazepam, meprobamate, and meperidine); (b) Rarely Appropriate (some indications for appropriate use; 8 drugs including propoxyphene, diazepam, cyclobenzaprine, carisoprodol, methocarbamol, and chlordiazepoxide); or (c) Some Indications (most use is considered inappropriate; 14 drugs including amitriptyline, promethazine, indomethacin, oxybutynin, hydroxyzine, and dipyrindamole).
Beers, 2003 ²⁹	Older adults in the community	Expert consensus panel of 12 members identified 48 individual drugs or classes to avoid regardless of diagnoses or conditions plus 20 diseases/conditions for which certain drugs should be avoided.
NCQA-HEDIS, 2006 ¹⁹	Older adults in the community	Expert consensus panel classified the 2003 Beers list into 3 categories: Always Avoid, Rarely Appropriate, and Some Indications. Drugs in the Always Avoid and Rarely Appropriate categories composed the 2006 HEDIS measure.

^aDeveloped in part from Pugh et al. (2006).¹⁹

AHRQ=Agency for Healthcare Research and Quality; HEDIS=Healthcare Effectiveness and Data Information Set; NCQA=National Committee for Quality Assurance.

addition to their finding of higher rates of cardiovascular risk for codeine compared with hydrocodone during the first 180 days of opioid therapy, Solomon et al. found similar risk of cardiovascular events for propoxyphene compared with 3 other opioids (hydrocodone, oxycodone, and tramadol) during both the first 30 days and 180 days of therapy.⁹ The FDA's decision was based in part on new data reported by the manufacturer of Darvon-Darvocet in July-August 2010 indicating that cardiac arrhythmias occurred at normal doses of propoxyphene, contradicting a previous assumption that cardiac arrhythmias occurred only at higher than recommended doses.^{14,17} Uncertainty about safety evidence for different opioids, such as that suggested by a comparison of the Solomon et al. findings with the manufacturer's study of propoxyphene, raises a broader question: how much do we know about which drugs are truly harmful for older patients?

Utilization of Potentially Inappropriate Medications (PIMs) in Older Adults: Are We Targeting the Right Drugs?

With implementation of the Medicare Part D drug benefit imminent on January 1, 2006, the National Committee for Quality Assurance (NCQA) announced in mid-2005 that it would adopt a list of "drugs to be avoided in the elderly" (DAE) as a quality measure for health plans in 2006.¹⁸ The Healthcare Effectiveness and Data Information Set (HEDIS) DAE list in 2006 represented a subset of a drug list derived from the work of a 2003 expert panel (Table 1). The 2003 panel classified 48 drugs/classes into 3 categories: Always Avoid, Rarely Appropriate, and Some Indications; the NCQA-HEDIS 2006 list was composed of 42 drugs that had been classified as Always Avoid or Rarely Appropriate in 2003.¹⁹ The NCQA-HEDIS 2006

list of DAEs omitted several common drugs (e.g., amitriptyline and doxepin) that had been defined as PIMs by previous expert consensus panels in both the Beers list (1997) and the updated Beers list (2003). Also omitted from the NCQA-HEDIS 2006 DAE list were several commonly used drugs that were rated "high" in severity of adverse effects on the 2003 Beers list, including 4 NSAIDs (indomethacin, naproxen, oxaprozin, and piroxicam), fluoxetine, amiodarone, methyldopa, and short-acting oxybutynin.

In 2002, Gurwitz and Rochon suggested that the Beers criteria may be inappropriate to measure PIM use in the elderly because the list includes many drugs that were once common but no longer considered by many prescribers, such as flurazepam (Dalmane), pentazocine (Talwin) and meprobamate (Equanil/Equagesic).²⁰ More than 8 years later, these drugs and most of the Beers criteria drugs accounted for much of the NCQA-HEDIS 2009 and 2010 lists of DAE "high-risk medications."^{21,22} Missing from this current list of DAE-PIMs are common opioids that perhaps pose greater threat to patient safety among older adults; for example, codeine (e.g., with acetaminophen) is not included except in combination with antihistamines or skeletal muscle relaxants.

Skepticism about the degree to which PIMs are truly harmful, or perhaps provider perceptions that PIMs meet therapeutic needs that could not otherwise be addressed, are suggested by examination of trend data for use of PIMs. For example, resistance to reduction in use of PIMs in older adults is evident in the data reported by NCQA for Medicare beneficiaries. NCQA tracking of the prevalence of use of DAE high-risk medications shows no change over the 4-year period from 2005 to 2008 (Table 2). Approximately 23%-24% of Medicare beneficiaries

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TABLE 2 Summary of Results of Selected Studies of PIM Utilization in Older Adults^a

Authors (Publication Date)	Description of Sample and Study Period	Definition of PIM	% (n) Receiving PIM	% Receiving Propoxyphene
Fick et al. (2001) ²⁵	1 HMO; n=2,336; June 1, 1997 - October 31, 1998	Beers list (1997)	23.2 (n = 541)	9.6 (n = 224)
Zhan et al. (2001) ²⁷	National survey data from NMCES (1987), MCBS (1992), and MEPS (1996)	Zhan (2001)	21.3 ^b	4.8 [1987-NMCES] 5.6 [1992-MCBS] 6.2 [1996-MEPS]
Pugh et al. (2005) ²⁶	National VA; n = 1,265,434; October 1, 1999-September 30, 2000	Zhan (2001) plus dose-limited drugs ^c	23.0 [17.5] ^{c,d}	4.1
Pugh et al. (2006) ¹⁹	National VA; n = 1,096,361; October 1, 1999 - September 30, 2000	HEDIS 2006	19.6 ^e	4.5
Barnett et al. (2006) ³¹	10 private HMOs; n = 157,517; January 2000-June 2001	Zhan (2001); 33 drugs	28.8 (n = 45,365)	7.0 (n = 11,034) ^f
Barnett et al. (2006) ³¹	VA (10 regions); n = 123,633; April 2002 - September 2003	Zhan (2001); 33 drugs	21.3 (n = 26,339)	3.0 (n = 3,692) ^g
NCQA 2005 ²³	National reporting - 2005	HEDIS DAE	23.9 [6.6] ^d	NR
NCQA 2006 ²³	National reporting - 2006	HEDIS DAE	23.1 [5.9] ^d	NR
NCQA 2007 ²³	National reporting - 2007	HEDIS DAE	23.2 [6.0] ^d	NR
NCQA 2008 ²³	National reporting - 2008	HEDIS DAE	23.4 [6.0] ^d	NR
Zhang et al. (2010) ²⁴	Medicare Part D beneficiaries (n = 533,170) in calendar year 2007	HEDIS DAE ^h	25.8	-
NDHCRI ³³	Medicare Part D beneficiaries in North Dakota who filled at least 1 prescription during the 6 months from April 1, 2008, through September 30, 2008	CMS 2008	14.8	5.1
SDFMC ³³	Medicare Part D beneficiaries in South Dakota who filled at least 1 prescription during the 6 months from April 1, 2008, through September 30, 2008	CMS 2008	16.4	7.2

Intervention to Reduce PIM Utilization

Kaufman et al. (2005) ⁴⁴	1 HMO (New York); n = 90,000-100,000 1999 Q4-2001 Q4	8 contraindicated drugs ⁱ	5.3 ^j (n = 2,871) in 1999 Q4 (baseline); 4.3 ^j (n = 2,713) in 2001 Q4	NR
Kaufman et al. (2005) ⁴⁴	1 HMO (New York); n = 100,000-110,000 2002 Q1-2003 Q4	10 contraindicated drugs ^k	2.4 ^j (n = 1,495) in 2002 Q1; 2.2 ^j (n = 1,451) in 2003 Q4	NR

^aAll studies selected persons aged 65 years or older.

^b2.6% received at least 1 of 11 Always Avoid drugs; 9.1% received at least 1 of 8 Rarely Appropriate drugs; and 13.3% received at least 1 of 14 Some Indications drugs.

^cPIMs in this study included 7 drugs (digoxin and 6 short-acting benzodiazepines, such as alprazolam) defined by the Zhan-AHRQ panel as dose-limited, and 16.1% received at least 1 dose-limited drug, and the prevalence was 4.6% after adjustment for diagnosis, dose, and duration. Prevalence rates before (after) adjustment for diagnosis, dose, and duration for the 3 Zhan categories were: 0.8% (0.8%) of beneficiaries received 1 or more of 11 Always Avoid drugs, 8.9% (8.0%) received at least 1 Rarely Appropriate drug, and 15.5% (13.3%) received at least 1 Some Indications drug.

^dThe numbers in [] are the proportions of health plan members who received 2 or more DAEs.

^ePugh et al. (2006) excluded the HEDIS 2006 estrogen drugs because their study period (1999-2000) preceded publication of the Women's Health Initiative study results which changed recommendations for use of estrogens in certain women. Even with the exclusion of estrogens, 23.3% of women versus 19.2% of men had received at least 1 drug on the HEDIS 2006 list of DAEs.

^fThe rate of propxoxyphene use among females was 8.5% versus 5.0% among males; this private sector HMO population was 56.5% female (n = 88,970 of 157,517 members).

^gThe rate of propxoxyphene use among females was 4.9% versus 2.0% among males; this VA sample was 2.7% female (n = 3,311 of 123,633 beneficiaries).

^hZhang et al. did not include the "narcotics" (propxoxyphene, meperidine, pentazocine, opium, and naloxone) from the HEDIS 2009 list. Result shown is the mean value for hospital referral regions.

ⁱThe 8 drugs defined as contraindicated based on the Beers list (1997) were: amitriptyline, cyclobenzaprine, diazepam, indomethacin, meprobamate, methocarbamol, methylidopa, and propxoxyphene (including combinations).

^jThe denominator in these proportions was the count of utilizing members, approximately 65% of eligible members, by calendar quarter.

^kThe 10 drugs defined as contraindicated based on Zhan (2001) were: amitriptyline (in doses 50 mg per day or more), cyclobenzaprine, diazepam, indomethacin (2 or more pharmacy claims in the calendar quarter), meprobamate, methocarbamol, methylidopa, dicyclomine, disopyramide, and hyoscyamine (i.e., excluding propxoxyphene and combinations).

AHRQ = Agency for Healthcare Research and Quality; CMS = Centers for Medicare & Medicaid Services; DAE = Drugs to Avoid in the Elderly; HEDIS = Healthcare Effectiveness Data and Information Set; HMO = health maintenance organization; MCBS = Medicare Current Beneficiary Survey; MEPS = Medical Expenditure Panel Survey; mg = milligrams; NDHCRI = North Dakota Health Care Review, Inc., the Medicare QIO for North Dakota; NMCES = National Medical Care Expenditure Survey; NR = not reported; PIM = potentially inappropriate medication; QIO = quality improvement organization; SDFMC = South Dakota Foundation for Medical Care, the Medicare QIO for South Dakota; VA = Veterans Affairs.

received at least 1 of the DAEs each year, and approximately 6% received 2 or more DAEs each year.²³ But, there is apparently some geographic variation in DAE use. In November 2010, Zhang et al. reported that the rates of utilization of DAEs varied by nearly 4-fold from 11.4% of Medicare Part D beneficiaries in the Bronx, New York, to as much as 44.0% of beneficiaries in Alexandria, Louisiana.²⁴ This research also found that variation in DAE utilization was not related to overall spending on drugs (Pearson correlation [r]=0.02, P =0.78), meaning that the quality of prescribing, assessed via the use of DAEs, was not associated with higher use and spending for all drugs. Additionally, DAEs accounted for less than 1% of total drug expenditures. However, DAE use was associated with higher medical expense (r =0.30, P <0.001).

Utilization rates of PIMs in older adults have remained high for nearly 2 decades even though the composition of the lists of PIMs has changed; and most research has found high rates of PIM use for members of managed care organizations. Based on the original (1997) Beers criteria for ambulatory care, Fick et al. found that 541 of 2,336 continuously enrolled beneficiaries (23.2%) in a managed Medicare health maintenance organization (HMO) received 1 or more PIMs during the 17-month period from June 1, 1997, through October 31, 1998²⁵ (Table 2). Propoxyphene (and its combination products, primarily with acetaminophen) was received by 41.4% (n =224) of the 541 beneficiaries who received 1 or more PIMs; other commonly used PIMs were amitriptyline (n =73), cyclobenzaprine (n =49), hydroxyzine (n =37), diazepam (n =36), promethazine (n =33), carisoprodol (n =31), and indomethacin (n =29). Data from 2 years later in a national sample of nearly 1.3 million Veterans Affairs (VA) beneficiaries aged 65 years or older for the period from October 1, 1999, through September 30, 2000, found a 23.0% overall prevalence of PIMs defined by the Zhan (2001) criteria, including 0.8% Always Avoid, 8.9% Rarely Appropriate, and 15.5% Some Indications.²⁶ A separate study of nearly 1.1 million VA beneficiaries aged 65 years or older for the same 12-month period from October 1, 1999, through September 30, 2000, found a 19.6% overall prevalence of PIM use using the NCQA-HEDIS 2006 list of DAEs to define PIMs.¹⁹

In both VA samples, propoxyphene was the highest use PIM (Table 2). In the study of approximately 1.1 million VA beneficiaries (98% male), 4.5% received propoxyphene at least once in the 12-month period (5.7% of females and 4.5% of males). A nearly identical rate of propoxyphene use (4.1%) was found in the study of nearly 1.3 million VA beneficiaries (also 98% male) for the same 12-month period. In the latter study, 51.9% of the VA beneficiaries who received propoxyphene had also received the drug in the preceding year.²⁶

Aside from propoxyphene being the most common PIM in the managed Medicare study described Fick et al. and in the 2 studies approximately 2 years later in VA beneficiary samples,

there was more discrepancy than overlap in the prevalence of use of specific PIMs. There was similarity in the prevalence of use of diazepam (1.2% and 1.5% in the 2 VA samples and 1.5% in the Medicare HMO) but wide variation for most other PIMs. For example, the second most common PIM in the VA sample of 1.1 million beneficiaries was diphenhydramine, received by 3.5% of male and 4.7% of female beneficiaries, versus 0.1% of Medicare HMO members studied by Fick et al.^{25,26} Chlorpheniramine, another common antihistamine, was received by 2.1% of the VA population versus 0.3% of the Medicare HMO members.^{25,26} The disparity in use of these PIMs among VA beneficiaries versus Medicare HMO members may be attributed to differences in coverage (e.g., diphenhydramine and chlorpheniramine may have been excluded from coverage as over-the-counter drugs in the Medicare HMO and therefore not captured in pharmacy claims data). These examples suggest that caution is warranted when attempting to evaluate prevalence of use of specific PIMs across samples and that factors other than prescribing practices may explain variation in PIM use (e.g., drug coverage policies, formulary management, or nuances in claims administration or record-keeping practices).

Resilient Use of Propoxyphene

The survival of propoxyphene on the U.S. market through decades of controversy over its safety underscores the challenge in identifying drugs that are truly inappropriate and should not be prescribed, particularly for older adults. The Zhan criteria (2001), developed by a 7-member expert panel including geriatricians, a pharmacoepidemiologist, and a pharmacist under funding from the Agency for Healthcare Research and Quality (AHRQ), classified propoxyphene as “rarely appropriate” rather than “always avoid” because although it was judged never appropriate as a new drug for pain, it may be appropriate for continued use by a patient who has demonstrated tolerance for the drug, “is not abusing it, and expresses a strong preference” for continued use.²⁷ The Beers criteria expert panel in 1997 classified the severity of adverse effects associated with propoxyphene as “not high,”²⁸ and the Beers 2003 criteria classified propoxyphene severity of adverse effects as “low.”²⁹ The prevalence of propoxyphene use in older adults has been persistent despite its inclusion in the HEDIS list of DAEs from the NCQA since 2006^{18,19,21,22} and assessment of the DAE utilization rate as a quality measure for health plans including all Medicare managed care contractors.³⁰

The analyses of PIM prevalence reported by Zhan et al. as part of the AHRQ-funded development of a 3-category, 33-PIM list found that propoxyphene utilization, measured as the percentage of community-dwelling elderly receiving propoxyphene, rose from 4.8% in the 1987 National Medical Care Expenditure Survey, to 5.6% in the 1992 Medicare Current Beneficiary Survey, and 6.2% in the 1996 Medical Expenditure

Panel Survey (Table 2). Over an 18-month study period from January 2000 to through June 2001, Barnett et al. found that 7.0% (n=11,034) of 157,517 Medicare beneficiaries enrolled in 10 private HMOs received at least 1 prescription for a propoxyphene product.³¹ Propoxyphene was the highest-use PIM in this study of older adults in managed care, and more women (8.5%) than men (5.0%) had records of propoxyphene use. In a later 18-month period from April 2002 through September 2003, 3.0% (n=3,692) of 123,633 VA beneficiaries aged 65 years or older in 10 regions of the country received at least 1 prescription for propoxyphene, with similar rates of propoxyphene use among males (3.0%) and females (3.6%).³¹ The lower rate of propoxyphene use in this VA sample of older adults in 2002-2003 is likely attributable to the nonformulary status of propoxyphene (information about propoxyphene's formulary status in the Medicare HMOs was not available). However, despite its nonformulary status, propoxyphene was dispensed to at least 3.0% of VA beneficiaries, and the actual utilization of propoxyphene was probably much higher because medications dispensed by non-VA pharmacies were not recorded in the VA database.

More recent data show that propoxyphene continued to account for a large share of PIM use in the Medicare Part D program. For example, the quality improvement organization (QIO) for Florida reported that propoxyphene including combination with acetaminophen accounted for almost one-third of all PIMs in Medicare Part D claims in Florida in the last 6 months of 2007,³² and the QIO for North and South Dakota reported that propoxyphene was received by approximately 5% of Medicare Part D beneficiaries or 35% of all PIMs in North Dakota in the 6 months through September 30, 2008.³³ In South Dakota, propoxyphene was received by approximately 7.2% of Medicare Part D beneficiaries or 44% of all PIMs, nearly the same proportion as the 41% of PIMs reported by Fick et al. in a managed Medicare population 10 years earlier.²⁵

Actual Harm Versus Predicted Harm – High Noise-to-Signal Ratio

There is a distinct lack of consensus on which drugs pose an increased risk of harm, and the dissonance can be large. For example, previous research showed that 59% of 46 preventable drug-related morbidity (PDRM) factors accepted by expert panels in the U.S. were rejected by expert panels in the U.K.³⁴ Such disagreement among experts is understandable because new evidence is constantly emerging, and circumstances differ among practice settings. Among the 27 PDRM factors accepted by panel experts in the U.S. but rejected in the U.K. were (a) use of a tricyclic antidepressant; and (b) the risk of liver toxicity associated with troglitazone (Rezulin), the latter because troglitazone had already been withdrawn from the market in the U.K.³⁵ From this perspective, lists such as DAE from NCQA and PIMs should not be viewed as definitive indicators

of population-level harm, but instead provide guidance for evaluation of the appropriateness of use in *individual* cases and opportunities for continuous evaluation of the evidence that supports the association between PIM exposure and actual patient harm. As suggested in the 2 reports from Solomon et al. in December 2010 and the recent evidence of unexpected harm associated with rosiglitazone and bisphosphonates, studying the relationship between suspected and actual harm associated with drug therapy should be an ongoing, continuous quality improvement process.

Steinman et al. (2009) assessed the appropriateness of drug use at the Iowa VA Medical Center in 256 elderly outpatients using 5 or more medications, finding little concordance between PIM criteria and actual “problematic” drug use as assessed by a physician-pharmacist team.³⁶ The team identified 563 of 3,678 drugs (15.3%) received by the 256 elderly outpatients as “problematic,” versus 214 PIMs (5.8%) according to the Beers criteria and 91 (2.5%) by the Zhan criteria. The expert reviewers rejected as nonproblematic 61% of the Beers criteria PIMs and 49% of the Zhan criteria PIMs. In other words, this analysis found false-positive rates for Beers and Zhan criteria of 61% and 49%, respectively, and both lists had large false-negative rates for “problematic prescribing.”

Beers PIMs Do Not Predict ER Visits for ADEs in Older Adults

Although there is considerable research reported for the use of PIMs, there is surprisingly little reported on actual harm manifest as adverse drug events (ADEs). The disparity between noise and true signal in PIMs was investigated by Budnitz et al. (2007) using a national public surveillance sample of hospital emergency room (ER) visits in 2004 and 2005 for persons aged 65 years or older. Based on a sample of 4,492 ER visits for ADEs, Budnitz et al. estimated that 177,504 ER visits associated with ADEs in elderly patients occurred in the United States in each of the 2 study years.³⁷ Of the total estimated ADE-related ER visits per year, only 6,452 (3.6%) were attributed to the 41 drugs defined as “always potentially inappropriate” in the most recent (2003) list (e.g., indomethacin, cyclobenzaprine, propoxyphene). A higher estimated number of ER visits (n=9,308) was associated with the 7 Beers list drugs defined as “potentially inappropriate in certain circumstances” (e.g., daily fluoxetine, naproxen, short-acting benzodiazepines such as alprazolam at doses of more than 2 milligrams [mg]). In contrast, 3 drugs *not* on the Beers list of drugs defined as always potentially inappropriate accounted for 33.3% of the ADE-related ER visits: warfarin (17.3%), insulin (13.0%), and digoxin (3.2%). Although lower in severity than the digoxin-associated ADE-related ER visits (80% of which resulted in hospitalization), an additional 10.4% of ER visits were associated with aspirin (5.7%) or clopidogrel (4.7%). In the context of actual outpatient use of all drugs, the risk of ADE-associated ER visits was 35 times higher for warfarin,

insulin, and digoxin combined than for the Beers list of PIMs considered to be always potentially inappropriate (206 versus 5.6 per 100,000 outpatient prescription visits).³⁷ This evidence suggests that efforts to improve patient safety in drug therapy in older adults would be better spent in diligent monitoring of drugs known to be associated with harmful ADEs rather than “prescriber education” about PIMs.

The important work reported by Budnitz et al. substantiates the risk of potential harm posed by propoxyphene, but the risk is small from a population perspective. The 0.5% of ER visits associated with propoxyphene ADEs, and the same rate for nitrofurantoin, placed these 2 drugs behind the anticholinergics and antihistamines (0.9%) in the proportion of ADE-related ER visits attributable to the 41 Beers list PIMs that are defined as always potentially inappropriate.³⁷ However, this rate for propoxyphene means that it accounted for only about 1 in 200 ADE-related ER visits in 2004-2005, less than the 0.6% of ER visits attributed to naproxen and piroxicam combined. In other words, the market withdrawal of propoxyphene will have a large impact on the proportion of patients who receive PIMs, but it will probably not have a perceptible effect on the number of ADE-related ER visits.

Specific Drugs Related to Hospital Admissions

There is surprisingly little published research regarding the specific drugs that are most commonly responsible for drug-related hospital admissions. In a systematic review, Howard et al. (2006) found 17 prospective observational studies that described the proportion of hospital admissions that were drug-related and preventable and either the types of medications or underlying causes associated with preventable drug-related admissions.³⁸ A median 3.7% (range 1.4%-15.4% in 13 studies) of hospital admissions were found to be drug-related and preventable, and 51% of the preventable drug-related admissions involved 4 classes of drugs (9 studies): antiplatelets (16.0%), diuretics (15.9%), NSAIDs (11.0%), anticoagulants (8.3%), or opioid analgesics (4.9%). Four of the studies evaluated by Howard et al. included patients aged 65 years or older, and 2 small studies of elderly patients found 12.0% of 150 hospital admissions³⁹ and 15.4% of 240 hospital admissions⁴⁰ to be drug-related and preventable, but an additional larger study found 4.3% of 1,011 hospital admissions to be drug-related and preventable.⁴¹

The systematic review by Howard et al. also provides some information regarding the underlying causes of hospital admissions attributable to preventable ADEs. Across 5 studies in which ADE-related hospital admissions were examined for underlying cause, a median 33.3% were attributed to problems with patient adherence, 22.2% to inadequate monitoring, and 30.6% to problematic prescribing; 12.5% of ADE-related admissions were unclassified as to cause.³⁸ The work reported by Gandhi et al. for ADEs reported by ambulatory care patients

suggests that there is considerable opportunity for clinicians to be more attentive to medication-related symptoms for the 11.0% of ADEs that were deemed preventable.⁴²

One Step Forward or 2 Steps Backward in Protecting Patients from ADEs?

Collectively, the 2 studies reported by Solomon et al. in December 2010 advance knowledge of the relative harms and benefits of 3 classes of drug therapy commonly used in older adults and for individual drugs in the opioid class. One study challenges the theory that opioid analgesics are safer than non-opioid analgesics in the elderly,⁸ and the second study suggests that the individual opioids pose different risks across the spectrum of adverse events. Compared with hydrocodone, codeine was associated with increased risk of cardiovascular events, and tramadol and propoxyphene may pose less risk of fracture compared with hydrocodone.⁹ The latter finding contradicts research now nearly 20 years old that found a similar risk for hip fracture for propoxyphene and hydrocodone.⁴³ The action by the FDA in November 2010 to remove propoxyphene from the U.S. market will seemingly have uncertain effects in protecting patient safety. We do know from the work of Budnitz et al., however, that hydrocodone-acetaminophen accounted for 1.7% of ADE-related ER visits, more than 3 times the number of ER visits associated with propoxyphene ADEs.

From one perspective, it can be argued that the recent research reported by Solomon et al. in 2 studies raises more questions than it answers. On the other hand, although we don't necessarily know with a degree of certainty which drugs are less harmful in older adults, it seems that we now know more about the magnitude of what we don't know in this regard. And importantly, it is increasingly inescapable that the rewards in improved patient safety will derive from increased attention from pharmacists and physicians to continuous monitoring of patient response to drug therapy, particularly for chronic drug therapy in older adults.

Managed Care Interventions to Reduce Prevalence of PIMs

Among the managed care interventions that have been conducted with the intent to reduce the use of PIMs in older adults was a 4-year, 3-pronged effort reported in *JMCP* in 2005 by Kaufman et al.⁴⁴ This intervention was conducted in a large HMO that included approximately 100,000 Medicare members with pharmacy benefits. After each calendar quarter over 4 years of the intervention, prescribers of certain PIM drugs received lists of their patients, the specific drugs dispensed to these patients, and suggestions for formulary therapeutic alternatives. In addition to the letters and patient drug profiles sent by mail, a clinical pharmacist called high-volume prescribers (i.e., those with 4 or more patients with PIMs in a given calendar quarter) by telephone to discuss therapeutic alternatives. The third prong of the intervention involved a 1-time general

mailing to all network physicians and pharmacists of an article in the HMO's pharmacy and therapeutics committee's newsletter on the subject of "inappropriate prescribing in the elderly." The mail and telephone interventions involved 8 target drugs defined as contraindicated based on the Beers list in calendar years 2000 and 2001 and 10 target drugs based on the Zhan list in calendar years 2002 and 2003 (Table 2). Although the authors had an ambitious goal of 0% use of the 8-10 contraindicated drugs, the first 2 years of the intervention were associated with little change, from 5.3% (n=2,871) of 54,211 pharmacy benefit users receiving 1 or more contraindicated drugs in the base period in 1999 Q4, to 4.3% (n=2,713) of 62,883 pharmacy benefit users receiving 1 or more contraindicated drugs in 2001 Q4.

The most noticeable change in the count of patients who received PIMs occurred after January 1, 2002, when the list of drugs was changed from 8 drugs to 10 drugs by (a) deleting propoxyphene (and combinations) from the target list, (b) increasing the threshold dose of amitriptyline to at least 50 mg per day, and (c) adding 3 drugs (dicyclomine, disopyramide, and hyoscyamine) to the target list.⁴⁴ Although the use of propoxyphene was not reported separately in this study, the deletion of propoxyphene from the target PIMs (and addition of dicyclomine, disopyramide, and hyoscyamine), was associated with PIM use prevalence of 2.4% in the first quarter (2002 Q1) and a stable rate of 2.2% utilization of the 10 target PIMs over 4 calendar quarters in 2003. It is important to note, however, that this intervention reported by Kaufman et al. for a Medicare + Choice (now Medicare Advantage) plan captured utilization rates for calendar quarters, compared with 12-month or 18-month utilization rates for much of the other research in the literature on the prevalence of PIM use in older adults. Second, because Kaufman et al. reported utilization rates for pharmacy benefit users, these rates should be multiplied by about 0.65 to estimate utilization rates for eligible members; therefore, the pre-intervention rate in 1999 Q4 was about 3.4% for the 8 target PIMs that included propoxyphene, compared with about 2.8% in the second year of the intervention (2001), and about 1.4% in the fourth year of the intervention (2003) for the 10 target PIMs that excluded propoxyphene.

Interventions with Prescribers Have Limited Effect in Reducing PIM Use

In theory, it should be simple to reduce the threat to all patients posed by high-risk drug therapy, particularly in older patients who are at higher risk of gastrointestinal bleeding and fractures or other injury associated with falls. After all, that is what *managed care* implies—managing care to improve clinical, service-humanistic, and cost outcomes. But, as Graf reminds us, there is a large demand for relief from chronic pain, reported by about 50% of the population, and this demand increases with age.¹³ The path toward optimum balance between harm and

benefit must surely pass through the valley of pain relief without risk of harm from gastrointestinal erosion or falls due to orthostatic hypotension or impaired reaction time. We are still looking for "the most important strategies that the nation can use to fight" the problem of inappropriate use of drugs in the elderly, as the DHHS described 9 years ago, while proclaiming that "provider behavior must be modified through education" along with "monitoring systems and patient and caregiver empowerment."¹²

In addition to the limited influence of a 3-part intervention to reduce utilization of 8-10 specific PIMs reported by Kaufman et al. in a managed Medicare population, other research has suggested that PIM use is resilient to prescriber interventions. Briesacher et al. (2005) found that the use of drugs defined as PIMs by the Centers for Medicare & Medicaid Services (CMS) was common among nursing home and assisted-living residents before and after these PIMs became subject to mandatory drug use review policy in July 1999.⁴⁵ These PIMs were found in 28.8% of nursing home residents and 22.4% of assisted-living residents before mandatory drug use review. PIM use was little changed in nursing home residents after mandatory drug use review (25.6%; 95% CI=24.1%-27.1%) and not significantly changed among assisted-living residents (19.0%; 95% CI=16.7%-21.3%). This research suggested that the small decline in PIMs among nursing home residents could not be attributed to the intervention, and the authors reported that "nearly all" pre-intervention use of the PIMs "came from medications with some acceptable indications."

PIM-DAE Identification is Only a Starting Point

The term "potentially inappropriate" should remind us that determination of prescribing problems and truly inappropriate medication use requires assessment of the characteristics of individual cases. In publishing their list of PIMs in older adults in 1997, Beers et al. cautioned that the list might be used as a screening tool or starting point for evaluation of the appropriateness of PIM use in individual patients.²⁸ In their later work to classify drugs into the 3 categories Always Avoid, Rarely Appropriate, and Some Indications (Table 1), the Zhan-AHRQ expert panel was split regarding classification of 5 muscle relaxants (carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, and methocarbamol). Some panel members judged that these 5 drugs should never be used in older adults because of lack of efficacy and the potential for adverse effects, but others argued that their use might be appropriate in a healthy older adult for a short course for acute back pain.²⁷

As we have noted previously, there is considerable disagreement among "experts" about what constitutes a potentially inappropriate drug and which drugs are truly contraindicated in older adults.⁴⁶ Nevertheless, the current NCQA-HEDIS quality of care measures for physicians include "use of high-risk medications in the elderly."⁴⁷ Crownover and Unwin reminded

us in 2005 that the path toward identifying potential threats to patient safety associated with prescription drug use in older adults began in a systematic way in 1991. Dubbed by Crownover and Unwin as BOGSAT (bunch of old guys sitting around talking),⁴⁸ Beers used a Delphi method with a panel of 13 experts to create the initial Beers list (1991) of PIMs for nursing home residents. Over the 20 years since this initial BOGSAT, almost all of the PIM-DAE lists have been developed by expert panels, generally using a consensus technique such as a Delphi method. However, expert consensus panels may or may not produce evidence-based guidelines for practice, leading Crownover and Unwin to opine that PIMs are not DIMs (definitely inappropriate medications) and that the PIM lists are inadequate because they do not suggest therapeutic alternatives for PIM targets, such as amitriptyline, that have an evidence base to support their use. And, given the lack of evidence of actual harm associated with much of the PIM-DAE “high-risk medication” list, it may be reasonable to raise the question of whether PIMs might be considered in the context of “no harm, no foul,” leaving a large opportunity for continuous and attentive monitoring for ADEs in all chronic drug therapy in older adults.

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DISCLOSURES

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