Evidence-Based Medicine: 
Which Drugs Are Truly Contraindicated for Use in Older Adults? 

Reading the manuscript by Kaufman, Almonosy, and Sarafian published in this issue of JMCP reminded me of the expression attributed to Niels Bohr (1885-1962), “An expert is a man who has made all the mistakes which can be made in a very narrow field.” The similarity of the outcomes of the Manhattan project and drug prescribing in older adults may not be immediately apparent.

Kaufman, Almonosy, and Sarafian in this issue of JMCP present data showing that sending letters to prescribers of drugs deemed to be contraindicated in older adults over a 4+ year intervention period was associated with a modest reduction in the incidence of such prescribing. Aside from the obvious inability to attribute this decline to the intervention, due to the absence of a control group, the intervention was associated with a change in the criteria for defining the target list of taboo drugs midway through the intervention period. This change in criteria, from a list based upon Beers’ ‘a list based upon Zhan et al.’, had the effect of creating a 2-part observation period: January 1, 2000, through December 31, 2001, and January 1, 2002, through December 31, 2003.

The change in criteria had more effect on the incidence of contraindicated drug use than did the prescriber intervention program in this managed care population of older adults. The incidence of contraindicated drug use declined from 5.3% in the preperiod (fourth quarter [Q] 1999) to 4.3% by the end of the first year of the intervention, in 2000 Q1. The incidence of drug use deemed to be inappropriate in this population remained unchanged at 4.3% over the second year of the intervention through 2001 Q4. It was not until the criteria were changed to Zhan et al. in 2002 Q2 that the incidence of taboo prescribing dropped, to 2.4% in the first quarter of 2002. The incidence of contraindicated drug use remained unchanged at 2.2% throughout the 4th year of the intervention.

The authors describe an intervention program that had an initial goal of zero (0%) incidence of use of drugs contraindicated in older adults. While perhaps inspiring at first mention, the experience in this managed care organization (MCO) over the 4-year period with 2 different sets of criteria defining the 2 lists of drugs highlights some of the potential shortcomings of some well-intentioned quality improvement goals. For example, use of the Beers criteria in the first 2 years of the intervention program resulted in letters to all physicians who prescribed amitriptyline to members of this MCO population, and amitriptyline was the highest-volume culprit among the drugs targeted as inappropriate for use in this population. The change to the criteria based upon Zhan et al. included acceptance of amitriptyline use in older adults up to 50 mg per day, and the amitriptyline use targeted by the intervention program fell off the radar. In a population of 2,336 Medicare members, according to the Beers criteria and a list of 37 drugs, 2,000,000 prescriptions for amitriptyline were dispensed to Medicare members aged 65 years or older. The prevalence of this use during 2000 and 2001 because amitriptyline was defined by the MCO experts as inappropriate? For all target drugs, the rate of physician action to change the drug (1.2%) and reduce the dose (1.7%), or discontinue the drug (12.5%) when appraised by the MCO of the potentially inappropriate medication (PIM) suggests that the rate of false-positive medication prescribers was 85% or more (when determined by physician opinion).

In addition to the matter of potentially false-positive instances in PIM in older adults, there is the equally important matter of false-negative or unidentified PIM instances. For example, Wagner et al. overturned conventional wisdom when they found in a study of 2,312 hip fractures in the New Jersey Medicaid program that short-acting benzodiazepines were no safer than long-acting benzodiazepines in risk of hip fracture; and Wang et al. found in a 6-month case-control study that zolpidem was no safer than the benzodiazepines, antipsychotics, or antidepressants in risk of hip fracture. Absent from the list of more than 50 “drugs to be avoided in the elderly” in the proposed measures for Health Plan Employer Data and Information Set (HEDIS) 2000 are zolpidem and the short-acting benzodiazepine alprazolam as well as indomethacin and amitriptyline.

Reports of the prevalence of PIM prescribing in older adults range from a frightening 37% to less than 4%, including potentially false-positive instances. Using the 1997 National Medical Expenditure Survey for 6,171 persons aged 65 years or older, Wilson et al. estimated that a 23.5% (95% confidence interval [CI], 22.4%-24.6%) of people aged 65 years or older living in the community, or 6.64 million Americans (95% CI, 6.28-7.10 million), received at least 1 of the 20 contraindicated drugs, the most common PIMs were diuretics, propoxyphene, amitriptyline, chlorpromazine, diazepam, indomethacin, and clorazapate, each used by at least half a million people aged 65 years or older. Including 3 controversial cardiovascular agents (propranolol, methyldopa, and reserpine) in the list of contraindicated drugs increased the incidence of PIM use to 32.9% (95% CI, 30.7%-33.1%), or 8.04 million people (95% CI, 8.64-9.44 million).

In a previous issue of JMCP, Flick, Waller, Maclean, et al. found a 23.2% prevalence of PIM use in a Medicare managed care population 541 Medicare members received one or more PIMs from June 1, 1997, through October 31, 1998, in a population of 2,336 Medicare members, according to the Beers criteria and a list of 37 drugs. Propoxyphene and combination products accounted for 9.6% of all PIMs in the study by Flick et al., followed by amitriptyline (3.1%), cyclobenzaprine (2.1%), hydroxyzine (1.6%), diazepam (1.5%), promethazine (1.4%), cariprenal (1.3%), and indomethacin (1.2%). Simon et al. found the prevalence of PIM to range from 23.0% to 36.5% among 10 health plans. Thus many older adults enrolled 157,517 older adults in 2000-2001. The prevalence
of PIM was 5% of elderly patients who received at least 1 of the 11 medications classified by Zhan as “always avoid,” and 13% received at least 1 of the 8 medications that would rarely be considered appropriate, including propoxyphene that alone accounted for an absolute prevalence of 7% among older adults enrolled in these 10 HMOs. Using data from the 1996 Medical Expenditure Panel Survey, Zhan et al. estimated from a population of 2,455 respondents aged 65 years or older that 21.3% (95% CI, 19.9%-23.1%) of community-dwelling elderly patients in the United States received at least 1 of 33 potentially inappropriate medications in 1996. Within the classifications of the expert panel, about 2.6% of elderly patients (95% CI, 2.0%-3.2%) used at least 1 of the 11 medications that should always be avoided by elderly patients; 9.1% (95% CI, 7.9%-10.3%) used at least 1 of the 8 that would rarely be appropriate; and 13.3% (95% CI, 11.7%-14.9%) used at least 1 of the 14 medications that have some indications but are often misused.

A study published last year evaluated a national sample of physician office visits and hospital outpatient department visits for patients aged 65 years or older during 1995 to 2000 according to 2 sets of criteria for inappropriate prescribing in older adults. Goulding found that 7.8% of patients received an inappropriate drug according to the Beers criteria in 2000, unchanged from 1995. When evaluated according to the Zhan et al. criteria, the rate of inappropriate prescribing in the elderly population was found to be 3.7% in 1995 and 3.8% in 2000, without any appreciable trend in the 5-year period. The Beers criteria were developed by an expert panel that identified 38 drugs or drug groups that generally should be avoided in elderly patients. The Zhan expert panel later narrowed the Beers list to 11 drugs or drug groups, of which 8 are almost always to be avoided in elderly adults.

The analysis by Goulding is significant for several reasons. One, this study showed that the prevalence of “inappropriate” prescribing in the elderly did not increase and, in fact, did not change in the 5-year period between 1995 and 2000, establishing reference points for others conducting research in smaller populations. Two, this study compared the application of 2 well-known sets of criteria for “inappropriate” drug prescribing with the same dataset and thereby informs us that the national rate is in the range of just less than 5% by the Zhan criteria and about twice as high according to the Beers criteria. Left for us to ponder and for the evidence police to determine is the rate of true potential harm to elderly patients attributable to inappropriate or poor prescribing, particularly among the noninstitutionalized adult population aged 65 years or older.

The American Medical Directors Association and the American Society of Consultant Pharmacists released a joint position statement in November 2004 that was critical of the Beers criteria for being developed by a panel of 12 experts rather than using a “recognized evidence-based methodology.” A popular and well-respected internist/physician opined in a clinical practice improvement project conducted in an HMO in the early 1990s that amitriptyline was a wonderful drug to influence mood and assist sleep when dosed at night-time in the appropriate older patient. This physician, who preferred amitriptyline to the selective serotonin reuptake inhibitors more popular among his younger colleagues, received some of the highest patient satisfaction scores among primary care physicians and later became the medical director for another HMO in the state. He was an outlier who would have received dozens of warning letters if the “expert” criteria for PIM had been applied to his practice, warning letters that are now believed to be idle-positive warnings and a potentially inappropriate intrusion on his clinical practice.

**Does Persistence With Drugs for Alzheimer’s Disease Matter?**

The National Institute for Clinical Excellence (NICE) in March 2005 may have pulled the rug out from under the issue of the value of treating Alzheimer’s disease (AD) with drugs in our current pharmacocologic armamentarium. The NICE Appraisal Committee was considering comments received through March 22, 2005, on its proposed recommendations: (1.3) “Donepezil, rivastigmine and galantamine are not recommended for use in the treatment of mild to moderate Alzheimer’s disease (AD).” (1.2) “Memantine is not recommended for the treatment of moderately severe to severe AD, except as part of ongoing or new clinical studies that are designed to generate robust and relevant data on long-term outcomes, due to the uncertainty of life and costs.” and (1.3) “People currently receiving donepezil, rivastigmine, galantamine and memantine, whether as routine therapy or as part of a clinical trial, may be continued on therapy (including at the conclusion of a clinical trial) until it is considered appropriate to stop.” Game, set, match.

The NICE appraisal of the 4 drugs currently available for the treatment for AD was thorough and definitive. As with much of what NICE produces, the opportunity for disagreement is small. But the NICE appraisal of the 4 available AD drugs represents both good news and bad news. We now have definitive guidance (the good news) for the appropriate use of AD drugs—there are no drugs (the bad news). AD is a devastating disease, now, in 2009, without effective drug treatment.

Tacrine (Cognex) was approved by the U.S. Food and Drug Administration (FDA) on September 9, 1993, for the treatment of mild-to-moderate dementia of the Alzheimer’s type. This cholinesterase inhibitor was followed by another, donepezil (Aricept), approved by the FDA on November 25, 1996, for the treatment of mild-to-moderate dementia of the Alzheimer’s type. Two other cholinesterase inhibitors followed, also...
approved by the FDA for the treatment of mild-to-moderate dementia of the Alzheimer’s type: rivastigmine (Exelon) on April 21, 2000,40 and galantamine (Reminyl) on February 28, 2001.41 Memantine (Namenda), with a different mechanism of action as a receptor antagonist for N-methyl-D-aspartate (NMDA), was approved by the FDA on October 16, 2003, for moderate-to-severe dementia of the Alzheimer’s type,42 including labeling that advised, ‘There is no evidence that memantine prevents or slows neurodegeneration in patients with Alzheimer’s disease.‘43

A systematic review and meta-analysis of the cholinesterase inhibitors in 2003 for 29 parallel-group or crossover randomized, double-blind, placebo-controlled trials published from January 1996 through December 2001 found (a) a modern effect on neuropsychiatric or functional outcomes in short-term randomized controlled trials, (b) no difference in outcomes among the various cholinesterase Inhibitors, and (c) no evidence of long-term effectiveness.44 The investigators searched for both published and unpublished trials and contacted researchers and pharmaceutical companies.

The next nail in the coffin for the use of the cholinesterase inhibitors for AD was driven one year later with the release in 2009 of the results of the long-term use of donepezil, for as long as 2 to 3 years. The AD2000 Collaborative Group concluded that donepezil was not cost effective with “benefits below minimally relevant thresholds.”45 In the AD2000 study, 365 community-resident patients with mild-to-moderate AD entered a 12-week run-in period in which they were randomly allocated donepezil (5 mg per day) or placebo. The 96 AD patients (86%) who completed the 12-week run-in period were randomized to either donepezil (5 mg or 10 mg per day) or placebo, with double-blind treatment continuing as long as judged appropriate. Primary end points were (a) entry to institutional care and (b) progression of disability, defined by loss of either 2 of 4 basic or 6 of 11 instrumental activities on the Bristol actives of daily living scale. No significant benefits were seen with donepezil compared with placebo in institution-alization (42% vs. 44% at 3 years, P = 0.4) or progression of disability (58% vs. 59% at 3 years, P = 0.4). The relative risk of entering institutional care in the donepezil group compared with placebo was 0.97 (95% confidence interval [CI], 0.72-1.30; P = 0.8). The relative risk of progression of disability or entering institutional care was 0.90 (95% CI, 0.74-1.24; P = 0.7). AD 2000 also found no significant differences between donepezil and placebo in behavioral and psychological symptoms, caregiver psychopathology, formal care costs, unpaid caregiver time, adverse events or deaths, or between 5 mg and 10 mg donepezil.

The results from AD2000 alone would appear to render moot the research findings on similar persistence with donepezil and rivastigmine described in this issue of CMCP by MacKnight et al.46–49 A long-term treatment (more than 6 months) with cholinesterase inhibitors is not associated with improvement in important clinical outcomes, including behavioral and psychological symptoms, caregiver psychopathology, formal care costs, unpaid caregiver time, adverse events, deaths, or entry to institutional care, what is the point of studying persistence or adherence to therapy? The NICCE Appraisal Committee appears to have closed the present chapter in the book on pharmacological treatment of AD, to the chagrin of AD patients and caregivers desperate for an intervention to slow or halt the progression of this disease.

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REFERENCE