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, 19.5%-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 of 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 1995.¹² 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 that should always be avoided plus 8 drugs that are rarely appropriate. The 5 most common inappropriate drugs were propoxyphene (1.5% of all older adults), hydroxyzine (1.1%), amitriptyline (0.7%), diazepam (0.7%), and oxybutynin (0.7%).

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 4% 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.”¹³ A popular and well-respected internal medicine 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 nighttime in the appropriate older patient.¹⁴ 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 false-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 pharmacologic armamentarium. The NICE Appraisal Committee was considering comments received through March 22, 2005, on its proposed recommendations: (1.1) “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, disease progression, quality 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.”¹⁵ 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 2005, 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.¹⁶ 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.^{17,18} 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, 2000,¹⁹ and galantamine (Reminyl) on February 28, 2001.²⁰ 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,²¹ including labeling that advised, "There is no evidence that memantine prevents or slows neurodegeneration in patients with Alzheimer's disease."²²

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 1966 through December 2001 found (a) a modest 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.²³ 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 2004 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."²⁴ In the AD2000 study, 565 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 486 AD patients (86%) who completed the 12-week run-in period were rerandomized 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 activities of daily living scale. No significant benefits were seen with donepezil compared with placebo in institutionalization (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 0.96 (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 *JMCP* by Mauskopf, Paramore, Lee, and Snyder.²⁵ If 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 NICE 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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Letters to the Editor

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Each letter should be signed by no more than 3 authors. Submissions must include your title, affiliation, complete mailing address, telephone number, and e-mail address. Potential bias or conflicts of interest must be disclosed.

Letters should be prepared in a word processing program, preferably Microsoft Word, and submitted electronically at jmcp.msubmit.net.