

Geriatric Pharmacotherapy Updates

David R.P. Guay, PharmD

Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota, and Division of Geriatrics, HealthPartners Inc., Minneapolis, Minnesota

NEUROLEPTIC-ASSOCIATED COMMUNITY-ACQUIRED PNEUMONIA IN THE ELDERLY

A population-based, nested case-control, epidemiologic study used the Dutch Integrated Primary Care Information database to evaluate whether use of typical or atypical neuroleptics was associated with the composite outcome of fatal or nonfatal community-acquired pneumonia in the elderly.¹ Two hundred fifty-eight case patients with incident (new-onset) pneumonia were matched with 1686 controls. Sixty-five (25.2%) case patients died within 30 days due to pneumonia. A dose-dependent increase in the risk of the composite outcome was noted with current use of either atypical neuroleptics (odds ratio [OR] = 2.61; 95% CI, 1.48–4.61) or typical neuroleptics (OR = 1.76; 95% CI, 1.22–2.53) compared with past use of neuroleptics. Use of atypical neuroleptics was associated with an increase in the risk of fatal community-acquired pneumonia only (OR = 5.97; 95% CI, 1.49–23.98). The risk of the composite outcome did not differ significantly between typical and atypical neuroleptics (OR = 1.48; 95% CI, 0.84–2.60). The risks associated with individual neuroleptic agents differed, with risperidone associated with the highest risk (OR = 3.51), followed by zuclopenthixol (not available in the United States) (OR = 2.25), haloperidol (OR = 1.95), olanzapine (OR = 1.90), and pipamperone (not available in the United States) (OR = 1.55). There was no clear pattern in the effect of duration of use, although for both classes of neuroleptics, the risk was highest during the first week; the ORs for ≤ 7 , ≤ 30 , and ≤ 60 days' use were 4.62 (95% CI, 2.05–10.38), 3.49 (95% CI, 1.88–6.50), and 3.13 (95% CI, 1.74–5.64), respectively, for atypical neuroleptics, and 2.41 (95% CI, 1.53–3.81), 2.10 (95% CI, 1.42–3.11), and 1.91 (95% CI, 1.31–2.78) for typical neuroleptics.

Editor's note: The results of this study support the previously noted association between neuroleptic use and pneumonia during analyses of the link between death and neuroleptic use in patients with dementia.² The possible mechanisms remain speculative. It is important to note potential limitations to the design of this observational trial. Selection bias, information bias, and residual confounding may have affected the findings. This study was performed in an outpatient setting; thus, the findings should not be extrapolated to elderly inpatients or residents of skilled nursing facilities. Studies of the differential effects of individual neuroleptics should be pursued based on these preliminary positive results.

References

1. Trifirò G, Gambassi G, Sen EF, et al. Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: A nested case-control study. *Ann Intern Med.* 2010;152:418–425.
2. US Food and Drug Administration. Public Health Advisory: Deaths with antipsychotics in elderly patients with behavioral disturbances. April 11, 2005. <http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/UCM053171.htm>. Accessed May 20, 2010.

DIFFERENTIAL EFFECTS OF ANTIHYPERTENSIVE CLASSES ON INTERINDIVIDUAL VARIABILITY IN HYPOTENSIVE RESPONSE AND STROKE RISK

A systematic review and meta-analysis of data from 389 clinical trials was performed to determine whether the differences in stroke reduction over a wide variety of antihypertensive agents/classes might be explained by differences in interindividual variability in the blood

Accepted for publication May 10, 2010.

Published online June 9, 2010.

© 2010 Excerpta Medica Inc. All rights reserved.

doi:10.1016/j.amjopharm.2010.06.001

1543-5946/\$ - see front matter

pressure (BP) response to these agents/classes. In trials that included an active comparator, more interindividual variability in the systolic BP (SBP) response was noted with angiotensin-converting enzyme inhibitors, angiotensin II-receptor blockers, and β -blockers (variance ratio [VR] = 1.08, 1.16, and 1.17, respectively; $P = 0.008$, $P < 0.001$, and $P = 0.001$). Less variability was noted with calcium channel blockers (CCBs) and non-loop diuretics (VR = 0.81 and 0.87, respectively; $P < 0.001$ and $P = 0.007$). In placebo-controlled trials, CCBs were associated with the lowest interindividual variability in SBP response (VR = 0.76; $P < 0.001$). The results were similar for parallel-group and crossover trials. Across all trials, the effects of treatment on interindividual variability in the SBP response ($r^2 = 0.328$; $P = 0.002$) accounted for the effects on stroke risk (OR = 0.79; 95% CI, 0.71–0.87; $P < 0.001$ for a VR ≤ 0.80). Both correlations remained significant when the 2 were combined in the same statistical model.

Based on these findings, the authors suggested that drug-class effects on interindividual variability in the BP response may account for differences in the effects of antihypertensive drugs on stroke risk, independent of their effects on mean BP.

Reference

Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: A systematic review and meta-analysis. *Lancet*. 2010;375:906–915.

RISK OF PROSTATE CANCER WITH DUTASTERIDE

The REDUCE (Reduction by Dutasteride of Prostate Cancer Events) study assessed the efficacy of dutasteride 0.5 mg/d in reducing the risk of incident biopsy-proven prostate cancer in men at increased risk for the disease.¹ The efficacy population numbered 8122 (4049 dutasteride, 4073 placebo). Of these individuals, 6729 (3305 dutasteride, 3424 placebo) had at least 1 prostate biopsy (study target was 2 biopsies, one at 2 years and another at 4 years); 6608 of these men had a biopsy at 1 to 24 months, and 4810 had a biopsy at 25 to 48 months. Among men having at least 1 prostate biopsy, cancer was detected over the 4-year study period in 659 men (19.9%) in the dutasteride group and 858 men (25.1%) in the placebo group (relative risk reduction [RRR] with dutasteride = 22.8%; 95% CI, 15.2%–29.8%; $P < 0.001$). Dutasteride therapy was associated with a significant reduction in Gleason grade 5–6 tumors compared with placebo in study years 1 and

2 (9.0% vs 12.0%, respectively; $P < 0.001$) and study years 3 and 4 (6.0% vs 9.2%; $P < 0.001$). However, in study years 3 and 4, dutasteride was associated with a significant increase in Gleason grade 8–10 tumors (0.5% vs <0.1%; $P = 0.003$). Dutasteride therapy was also associated with reductions compared with placebo in rates of acute urinary retention (1.6% vs 6.7%; RRR = 77.3%; $P < 0.001$), benign prostatic hyperplasia-related surgery (1.4% vs 5.1%; RRR = 73.0%; $P < 0.001$), and urinary tract infection (UTI) (5.3% vs 8.8%; RRR = 40.7%; $P < 0.001$). The following adverse events (AEs) were noted significantly more frequently in recipients of dutasteride compared with placebo: any drug-related AE ($P < 0.001$), drug-related AEs leading to discontinuation ($P < 0.001$), and the specific AEs of decreased libido ($P < 0.001$), loss of libido ($P = 0.03$), erectile dysfunction ($P < 0.001$), decreased semen volume ($P < 0.001$), and gynecomastia ($P = 0.002$). There was also an unexpected difference between dutasteride and placebo in the AE of cardiac failure (a composite of congestive heart failure, cardiac failure, acute cardiac failure, ventricular failure, cardiopulmonary failure, and congestive cardiomyopathy) (0.7% vs 0.4%; $P = 0.03$).

Editor's note: The results of this trial add to available data on the 5 α -reductase inhibitor (5-ARI) finasteride in the prevention of prostate cancer.^{2–4} In men without prostate cancer, 5-ARIs are used to treat lower urinary tract symptoms, producing dramatic shrinkage of the prostate (albeit over months of use) and reducing serum prostate-specific antigen (PSA) levels by $\geq 50\%$. However, in men taking a 5-ARI to prevent prostate cancer, the suppression of PSA levels can produce a false sense of security unless the PSA value is corrected (by multiplying year 0–2 PSA values by 2, year 2–7 values by 2.3, and year 8 values and beyond by 2.5) to estimate what the PSA level would have been if a 5-ARI had not been taken.⁵ A case could be made for performing a prostate biopsy any time the PSA level rises in a patient taking a 5-ARI, since, with an increase in PSA, the risk of cancer is increased 3-fold and the risk of high-grade cancer is increased 6-fold.⁶

In summary, the 5-ARIs do not prevent prostate cancer; they merely shrink tumors that have a low potential for lethality. In addition, these agents do not reduce the risk of prostate cancer in patients undergoing a prostate biopsy for cause (ie, for clinical indications, including an abnormal digital rectal examination or an abnormal PSA level corrected for the effect of the 5-ARI). The cancers that are “prevented” are limited to Gleason grade 5–6 tumors (ie, moderately well differentiated), which are less likely to be lethal than tumors

of higher grades. The lack of effect on high-grade tumors (Gleason grade 7–10) has been disappointing. Again, if the false sense of security associated with PSA suppression by 5-ARIs results in a delay in diagnosis of prostate cancer, patients may progress to high-grade disease that is difficult to cure.

References

1. Andriole GL, Bostwick DG, Brawley OW, et al, for the REDUCE Study Group. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med*. 2010;362:1192–1202.
2. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349:215–224.
3. Murtola TJ, Tammela TL, Määttänen L, et al. Prostate cancer incidence among finasteride and alpha-blocker users in the Finnish Prostate Cancer Screening Trial. *Br J Cancer*. 2009;101:843–848.
4. Thompson IM, Pauler Ankerst D, Chi C, et al. Prediction of prostate cancer for patients receiving finasteride: Results from the Prostate Cancer Prevention Trial. *J Clin Oncol*. 2007;25:3076–3081.
5. Etzioni RD, Howlader N, Shaw PA, et al. Long-term effects of finasteride on prostate specific antigen levels: Results from the prostate cancer prevention trial [published correction appears in *J Urol*. 2005;174:2071]. *J Urol*. 2005;174:877–881.
6. Thompson IM, Tangen CM, Goodman PJ, et al. Chemoprevention of prostate cancer. *J Urol*. 2009;182:499–507.

COMBINATION ANTIHYPERTENSIVE THERAPY AND RENAL OUTCOMES

The results of the ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension) trial have recently been published. Originally designed to have a mean follow-up of 5 years, the trial was terminated after a mean follow-up of 2.9 years as a result of the greater efficacy of benazepril + amlodipine ($n = 5744$) compared with benazepril + hydrochlorothiazide (HCTZ) ($n = 5762$). All randomized patients were included in the intent-to-treat analysis. There were 113 events of chronic kidney disease progression (2.0%) in benazepril + amlodipine recipients, compared with 215 events (3.7%) in benazepril + HCTZ recipients (hazard ratio [HR] = 0.52; 90% CI, 0.41–0.65; $P < 0.001$). The results were comparable when the analysis was restricted to subjects aged ≥ 65 years. In general, the hypotensive response was similar in the 2 groups. The most frequent AE in patients with chronic renal disease was peripheral edema (33.7% vs 16.0%, respectively; $P <$

0.001). In those with chronic renal disease, angioedema occurred more frequently in the benazepril + amlodipine group compared with the benazepril + HCTZ group (1.6% vs 0.4%; $P = 0.04$). In those without chronic renal disease, AEs that occurred significantly more frequently in the benazepril + HCTZ group than in the benazepril + amlodipine group were dizziness (25.5% vs 20.3%, respectively; $P < 0.001$), hypokalemia (0.3% vs 0.1%; $P = 0.003$), and hypotension (3.4% vs 2.3%; $P = 0.001$).

Editor's note: Differences in various end points have been observed between antihypertensive monotherapies, even when BP is lowered to the same extent. The results of this trial suggest that the same is true of combination therapies, depending on the agents used.

Reference

- Bakris GL, Sarafidis PA, Weir MR, et al, for the ACCOMPLISH Trial Investigators. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): A prespecified secondary analysis of a randomised controlled trial. *Lancet*. 2010;375:1173–1181.

INFLUENZA VACCINATION AND WARFARIN THERAPY

A randomized, placebo-controlled, crossover trial evaluated the effect of influenza vaccination on the international normalized ratio (INR) and weekly warfarin dose in 104 patients receiving stable warfarin regimens. Patients were randomized to a treatment sequence in which they either received influenza vaccine followed by placebo or placebo followed by influenza vaccine, each for 28 days, with a washout period of 14 days between periods. There were no significant differences in the mean INR (2.63 for vaccine-placebo sequence and 2.53 for placebo-vaccine sequence during vaccine periods; 2.67 and 2.63, respectively, during placebo periods) or mean weekly warfarin dose (31.91 and 30.27 mg during vaccine periods; 31.15 and 29.88 mg during placebo periods). After receipt of influenza vaccine or placebo, there were no significant changes in the mean warfarin requirement from the start of the study. The absence of any vaccination effect on the warfarin regimen was confirmed using a linear mixed-effects model for multilevel longitudinal data. Patients were within diagnosis-specific therapeutic INR ranges 72.4% and 70.7% of the time after receiving influenza vaccine and placebo, respectively ($P = \text{NS}$). There were no fatal or major bleeding events; there were 11 minor mucocutaneous hemorrhagic events (6 in vaccine periods; 5 in placebo periods).

Editor's note: Of 11 previous trials (5 retrospective, 6 prospective) of influenza vaccine in warfarin recipients, 7 found no interaction, 1 found a minor decrease in INR in older patients only, and 3 found a minor increase in INR. The results of the foregoing trial support the absence of a significant interaction between influenza vaccine and warfarin. Close and/or intensified INR monitoring does not appear to be necessary after influenza vaccination of patients receiving a stable, long-term warfarin regimen.

Reference

Iorio A, Basileo M, Marcucci M, et al. Influenza vaccination and vitamin K antagonist treatment: A placebo-controlled, randomized, double-blind crossover study. *Arch Intern Med.* 2010;170:609–616.

URINARY TRACT INFECTION TREATMENT AND WARFARIN THERAPY

The effect of antimicrobial therapy for UTI on bleeding risk in warfarin recipients was studied in a population-based, nested case–control analysis employing health care databases in Ontario, Canada (1997–2007). Cases were subjects aged ≥ 66 years who had been hospitalized for upper gastrointestinal tract hemorrhage. Ten age- and sex-matched controls were selected for every case subject. Adjusted ORs (AORs) were calculated for antimicrobial exposure within 14 days before upper gastrointestinal tract hemorrhage. The study population comprised 134,637 patients receiving warfarin, 2151 of whom had been hospitalized for upper gastrointestinal tract hemorrhage. Cases were almost 4 times more likely than controls to have received trimethoprim-sulfamethoxazole (AOR = 3.84; 95% CI, 2.33–6.33). Ciprofloxacin also was associated with an increased bleeding risk (AOR = 1.94; 95% CI, 1.28–2.95). No significant association was noted with amoxicillin/ampicillin (AOR = 1.37; 95% CI, 0.92–2.05), nitrofurantoin (AOR = 1.40; 95% CI, 0.71–2.75), or norfloxacin (AOR = 0.38; 95% CI, 0.12–1.26). With amoxicillin/ampicillin recipients as controls, trimethoprim-sulfamethoxazole use was associated with an almost 3-fold increase in bleeding risk (AOR = 2.80; 95% CI, 1.48–5.32). The study results support the use of antimicrobials other than trimethoprim-sulfamethoxazole and perhaps ciprofloxacin for the treatment of UTIs in older patients who are receiving warfarin.

Reference

Fischer HD, Juurlink DN, Mamdani MM, et al. Hemorrhage during warfarin therapy associated with cotrimoxazole

and other urinary tract anti-infective agents: A population-based study. *Arch Intern Med.* 2010;170:617–621.

OUTCOMES OF CONCOMITANT USE OF CLOPIDOGREL AND PROTON PUMP INHIBITORS

A retrospective cohort study employed data from the Tennessee Medicaid database to examine outcomes in patients with serious coronary heart disease who were receiving clopidogrel with or without a concurrent proton pump inhibitor (PPI). The data set included 20,596 patients, of whom 7593 were receiving combination therapy. Pantoprazole and omeprazole accounted for 62% and 9%, respectively, of PPI use. The adjusted incidence of hospitalization for gastroduodenal bleeding in users of combination therapy was 50% lower than that in users of clopidogrel only (HR = 0.50; 95% CI, 0.39–0.65). For those at highest risk of bleeding (≥ 3 recognized risk factors), concurrent use of clopidogrel and a PPI was associated with an absolute reduction of 28.5 hospitalizations for gastroduodenal bleeding per 1000 person-years (95% CI, 11.7–36.9). This effect was independent of PPI dose and was similar across the 5 PPIs in use at the time of the study. The HR for serious cardiovascular disease during PPI use was 0.99 for the entire cohort (95% CI, 0.82–1.19) and 1.01 for the subgroup who had undergone percutaneous coronary interventions with stenting during the qualifying hospitalization (95% CI, 0.76–1.34). This effect was also independent of PPI dose and was similar across the 5 PPIs. Contrary to expectations, there was no significant change in cardiovascular event rates during receipt of PPI therapy. However, the 95% CI did indicate a clinically important 19% increase in risk.

Reference

Ray WA, Murray KT, Griffin MR, et al. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: A cohort study. *Ann Intern Med.* 2010;152:337–345.

SALSALATE FOR TYPE 2 DIABETES

A double-blind, placebo-controlled, dose-ranging study evaluated the hypoglycemic, cardiovascular, and renal effects of salsalate, the nonacetylated prodrug of salicylate, in adults with suboptimally controlled type 2 diabetes. Patients were randomized to receive salsalate 3, 3.5, or 4 g/d or placebo for 14 weeks. Higher proportions of patients in the 3 salsalate groups had $>0.5\%$ decreases from baseline in glycosylated hemoglobin (HbA_{1c}) compared with those in the placebo group (44%, 54%, 60%, and 15%, respectively; $P = 0.009$).

The mean changes from baseline in HbA_{1c} in the salsalate 3, 3.5, and 4 mg/d groups were -0.36% ($P = 0.02$ vs placebo), -0.34% ($P = 0.02$ vs placebo), and -0.49% ($P = 0.001$ vs placebo), respectively. The 3 salsalate groups also had significant reductions compared with placebo in fasting glucose concentrations ($P < 0.001$), glycosylated albumin ($P < 0.001$), and triglycerides ($P = 0.005$), as well as a significant increase in adiponectin ($P < 0.001$). Mild hypoglycemia (documented blood glucose level ≤ 60 mg/dL and symptoms relieved by food) was more common in salsalate recipients than in placebo recipients, occurring in 22%, 30%, 22%, and 7% of the respective groups; however, this was noted only in subjects who were also receiving sulfonylureas. Urinary albumin concentrations were higher in salsalate recipients than in placebo recipients; the mean changes from baseline in the urine albumin-creatinine ratio were 4, 10, 19, and 3 $\mu\text{g}/\text{mg}$ creatinine, respectively, although only the changes in the salsalate 3.5- and 4-g/d groups were significant compared with placebo ($P = 0.032$ and $P < 0.001$, respectively). Salsalate was generally well tolerated; the most frequent AEs were mild heartburn, nausea, vomiting, and diarrhea. Tinnitus, a well-known effect of salicylates, occurred in 19% to 22% of salsalate recipients and 11% of placebo recipients.

Reference

Goldfine AB, Fonseca V, Jablonski KA, et al, for the TINSAL-T2D (Targeting Inflammation Using Salsalate in Type 2 Diabetes) Study Team. The effects of salsalate on glycemic control in patients with type 2 diabetes: A randomized trial. *Ann Intern Med.* 2010;152:346-357.

SUICIDE RISK WITH ANTICONVULSANTS

An observational cohort study evaluated the risks of suicidal acts and violent death with individual anticonvulsants in patients in the HealthCare Integrated Research database who were aged ≥ 15 years and initiated anticonvulsant therapy between July 2001 and December 2006.¹ Topiramate was used as the reference anticonvulsant, and analyses were conducted over 180- and 360-day periods. Among 297,620 new episodes of anticonvulsant treatment in 269,937 patients, the study identified 26 completed suicides, 801 attempted suicides, and 41 violent deaths (overall median follow-up, 60 days). The incidence of the composite outcome of completed suicide, attempted suicide, and violent death with ≥ 100 treatment episodes of anticonvulsant use ranged from 6.2 per 1000 person-years for primidone to 34.3 per 1000 person-years for oxcarbazepine.

Other high-risk agents included lamotrigine, tiagabine, and valproate (27.9, 29.5, and 25.6 per 1000 person-years, respectively). The risk of completed or attempted suicide was significantly increased with gabapentin (HR = 1.42; 95% CI, 1.11-1.80), lamotrigine (HR = 1.84; 95% CI, 1.43-2.37), oxcarbazepine (HR = 2.07; 95% CI, 1.52-2.80), tiagabine (HR = 2.41; 95% CI, 1.65-3.52), and valproate (HR = 1.65; 95% CI, 1.25-2.19). Analyses that included violent death had similar results. The increase in risk of completed or attempted suicide began within the first 30 days of treatment with each of the high-risk agents. In post hoc exploratory subgroup analyses in which carbamazepine was the reference anticonvulsant, gabapentin was associated with increased risks of suicidal events and the combination of suicidal acts and violent death in younger and older patients, patients with mood disorders, and patients with epilepsy or seizure disorders compared with users of carbamazepine. Oxcarbazepine and tiagabine were also associated with an increased risk in patients with mood disorders.

Editor's note: It should be noted that this was an exploratory analysis that sought to confirm and extend the observations of a meta-analysis conducted by the US Food and Drug Administration in 2008.² This study found that gabapentin, lamotrigine, oxcarbazepine, tiagabine, and valproate were the anticonvulsants associated with the highest risks of suicidal acts and/or violent death. However, at this time, the potential mechanisms of these effects are not understood. Furthermore, it is not clear at present how the clinician should make use of these data.

References

1. Paterno E, Bohn RL, Wahl PM, et al. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. *JAMA.* 2010;303:1401-1409.
2. US Food and Drug Administration. Statistical review and evaluation: Antiepileptic drugs and suicidality. <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf>. Accessed April 15, 2010.

LENIENT VERSUS STRICT RATE CONTROL IN ATRIAL FIBRILLATION

The RACE II (Rate Control Efficacy for Permanent Atrial Fibrillation: A Comparison Between Lenient Versus Strict Rate Control II) study enrolled patients with permanent atrial fibrillation who were treated with either lenient rate control, which targeted a resting heart rate < 110 beats/min ($n = 311$), or strict rate control, which targeted a resting heart rate < 80 beats/min and a heart rate < 110 beats/min during moderate

exercise ($n = 303$).¹ The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, bleeding, or life-threatening arrhythmic events. The estimated cumulative incidence of the primary outcome at 3 years was 12.9% in the lenient-control group and 14.9% in the strict-control group, with an absolute difference of -2 percentage points in the lenient-control group (90% CI, -7.6 to 3.5 ; $P < 0.001$ for the prespecified noninferiority margin [ie, the upper bound of the CI for the absolute difference between treatments in the estimated rate of the primary outcome was <10 percentage points]). The HR for the primary outcome in the lenient-control group compared with the strict-control group was 0.84 (90% CI, 0.58 to 1.21). The frequencies of the individual components of the primary outcome were similar in the 2 groups. Only the frequency of stroke was significantly different between groups (1.6% in the lenient-control group vs 3.9% in the strict-control group; HR = 0.35; 90% CI, 0.13 to 0.92). More patients in the lenient-control group than in the strict-control group met their heart-rate targets (304 [97.7%] vs 203 [67.0%], respectively; $P < 0.001$) in significantly fewer total visits (75 [median, 0] vs 684 [median, 2]; $P < 0.001$). The frequencies of symptoms and AEs were similar in the 2 groups. In these patients with permanent atrial fibrillation, lenient rate control was as effective as strict rate control and was easier to achieve.

Editor's note: This paper makes an important contribution to our understanding of the potential benefits and risks of strict ventricular rate control, as recommended by current guidelines.² Lenient and strict rate control had similar efficacy, although a much larger proportion of patients in the lenient-control group compared with the strict-control group achieved their target heart rate. This was also accomplished with lower doses of β -blockers, as well as a reduced need for combination atrioventricular nodal-blocker therapy. A lower AE burden might have been expected in the lenient-control group, although this was not the case. Of interest, 25% of patients in the strict-control group were unable to achieve target heart rates due to drug-related AEs. The potential clinical advantages of strict rate control may be offset by the AEs of the drugs used to achieve this control, particularly at higher doses.

Readers should be aware of the limitations of this study. The study duration may have been too short to observe a differential benefit that may require up to decades to become manifest. Patients with tachycardia-related cardiomyopathy, who present with very rapid

ventricular rates and heart failure, may receive particular benefit from strict rate control. This subgroup may have been underrepresented or not enrolled in RACE II. Data on symptoms and quality of life were insufficient to assess any effects of strict rate control on these domains. As in all randomized controlled trials examining the effects of rate and rhythm on embolic risk in atrial fibrillation and the effects of pharmacotherapy in normalizing rate and rhythm, selection bias may have skewed the study population toward those who were relatively well clinically, who were somewhat younger than the overall population with atrial fibrillation, and who had some degree of rate control at entry. Nonetheless, the results of this study should make it easier for clinicians to press for lenient rate control in frail elderly patients, thus avoiding uncomfortable and potentially lethal AEs.

References

1. Van Gelder IC, Groenveld HF, Crijns HJ, et al, for the RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010;362:1363–1373.
2. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol*. 2006;48:e149–e246.

CHANGES IN THE MARKETPLACE FOR ASTHMA AND COPD INHALERS

As a result of the need to comply with the Montreal Protocol on Substances That Deplete the Ozone Layer, several commonly used metered-dose inhalers containing chlorofluorocarbons will be phased out over the next 3 years. The affected products include nedocromil and metaproterenol inhalers (last date to manufacture, sell, or dispense: June 14, 2010); triamcinolone and cromolyn inhalers (last date to manufacture, sell, or dispense: December 31, 2010); flunisolide inhaler (last date to manufacture, sell, or dispense: June 30, 2011); and albuterol/ipratropium and pirbuterol inhalers (last date to manufacture, sell, or dispense: December 31, 2013).

Reference

- US Food and Drug Administration. Asthma and COPD inhalers that contain ozone-depleting CFCs to be phased

out; alternative treatments available [press release]. April 13, 2010. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm208302.htm>. Accessed May 17, 2010.

WARNING

Propylthiouracil—Although the risk of hepatotoxicity with propylthiouracil (PTU) has been known for many years, the FDA has only recently mandated the addition of a boxed warning to the prescribing information. PTU was approved in 1947 for the treatment of hyperthyroidism. However, it was not possible to assess its hepatotoxicity risk until the Adverse Events Reporting System (AERS) was instituted in 1969. In a recent evaluation of all reports of severe liver injury in the AERS (1969–June 2009) with PTU and the related drug methimazole, the FDA found 34 cases of severe liver injury associated with

PTU (23 adults and 11 children). Thirteen of the adult cases died and 5 required liver transplantation; 2 of the pediatric cases died and 7 required liver transplantation. Only 5 cases of severe liver injury were associated with methimazole (all in adults, 3 resulting in death). These data support the recommendation that use of PTU be reserved for patients who are unable to take methimazole or for patients in whom radioactive iodine or surgery is not appropriate.

Reference

US Food and Drug Administration. Information for Healthcare Professionals. Propylthiouracil-induced liver failure. June 4, 2009. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm162701.htm>. Accessed May 17, 2010.

Address correspondence to: David R.P. Guay, PharmD, College of Pharmacy, University of Minnesota, 7-115C Weaver-Densford Hall, 308 Harvard Street SE, Minneapolis, MN 55455. E-mail: guayx001@umn.edu