Update in New Medications for Primary Care

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General internists must capably prescribe hundreds of medications across multiple different categories. While most new drugs each year represent “me too” drugs that are simply new drugs within an existing class, a small number of drugs each year work through a completely novel mechanism and are potentially relevant for primary care practice. It is difficult to keep up with advances in pharmacotherapy and to obtain balanced information regarding comparative efficacy, side effects, and cost. In order to identify potentially relevant novel drugs, we searched the drugs@FDA database,¹ polled our institutional pharmacists, performed a lay Internet search for news stories, and reviewed the following journals for the period of January 1, 2009 through April 1, 2010: New England Journal of Medicine, Annals of Internal Medicine, ACP Journal Club, JAMA, Journal Watch, The Medical Letter, Medical Letter Treatment Updates, and the Lancet. We have chosen to discuss one recently approved drug and one novel drug in the pipeline: dronedarone for the treatment of atrial fibrillation and roflumilast as a controller medication for chronic obstructive pulmonary disease.

For the second half of this update, we identified new guidelines and reviews that aim to optimize our use of existing drugs for the treatment of common conditions in primary care. We used the same search strategy as that for new drugs and have elected to discuss osteoporosis, aspirin, and vitamin D. This paper derives from a presentation at the 33rd annual meeting of the Society of General Internal Medicine in April 2010.

NEW DRUGS

Dronedarone

Atrial fibrillation (AF) is the most common clinically significant arrhythmia. Its prevalence increases with age. For example, among individuals ≥ 80 years old, the prevalence is 9.0%.² The landmark AFFIRM study, published in 2002, demonstrated

that among patients who are anticoagulated to prevent stroke, 5-year mortality rates do not differ between patients randomly assigned to rate control versus rhythm control (21.3% vs 23.8%, $p=0.08$).³ Therefore, clinicians should use antiarrhythmic medication selectively, rather than routinely, for patients with atrial fibrillation. Indications include to: (1) alleviate symptoms in symptomatic patients, (2) prevent tachycardia-induced cardiomyopathy, (3) prevent hemodynamic compromise, and (4) improve exercise capacity. Amiodarone is commonly used for patients with an indication for antiarrhythmic therapy, particularly for those with an impaired ejection fraction. However, amiodarone has many serious potential side effects in long-term use, including pulmonary, thyroid, and hepatic toxicity.

Dronedarone is a new antiarrhythmic drug that is structurally similar to amiodarone except that it contains no iodine. It was approved by the FDA in July 2009. Dronedarone is a class 3 antiarrhythmic agent that works primarily as a slow and rapid potassium channel blocker. Like amiodarone, it also is an alpha and beta adrenergic antagonist. By adding a methyl sulfonamide group, it has a reduced half life (13–19 h) with less tissue accumulation than amiodarone.

The first trials to evaluate the efficacy of dronedarone were the EURIDIS and ADONIS trials, which were identical randomized controlled trials (combined $n=1,237$) of patients with at least one recent episode of atrial fibrillation (<3 months) who were in sinus rhythm at the time of randomization.⁴ Exclusion criteria included, among others, permanent AF, HR <50 (due to the beta-blocking properties of the drug), significant conduction disease, New York Heart Association (NYHA) class III or IV heart failure, chronic kidney disease, and baseline liver, pulmonary, or endocrine disease. Patients received dronedarone 400 mg twice daily or placebo for 1 year. The benefit of the drug was modest. At 12 months, most patients in each group had developed a recurrence of AF (67% vs 78%, respectively, $p=0.01$). Median time to first recurrence increased from 41 to 96 days. Mortality and hospitalization rates did not differ between the two groups. There was no observed thyroid, pulmonary, hepatic, or neurologic toxicity.

The next study was the ANDROMEDA trial of 627 patients who had been hospitalized with NYHA class III or IV heart failure.⁵ Notably, these were among the patients who were excluded in the EURIDIS and ADONIS trials. Only 25% of patients were in AF at study entry. At 2 months, mortality was 8.1% in the dronedarone group and only 3.8% in the placebo group. Most of the excess mortality was due to heart failure. Rates of hospitalization for cardiac causes and new onset renal dysfunction were also higher in the dronedarone group. The results were unexpected and prompted the FDA to deny a June 2005 new drug application for dronedarone. In 2009, investigators published the results from ATHENA; the

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study population (n=4,628) was more diverse than in the earlier trials and included patients with paroxysmal or persistent AF and at least one major risk factor for stroke. However, patients with NYHA class IV heart failure were excluded. The primary outcome of first hospitalization for cardiac causes or death was significantly less common among patients receiving the drug than among those receiving placebo (31.9% vs 39.4%, $p<0.001$). Mortality did not differ between the groups (5.0% vs 6.0%, respectively, $p=0.18$); however cardiovascular mortality was lower among patients receiving the drug (2.7% vs 3.9%, respectively, $p=0.03$). This large trial provided some comfort regarding the safety of longer term use of dronedarone in selected patients. Finally, the DIONYSOS trial, which has not yet been subjected to peer review, showed that dronedarone was inferior to amiodarone in maintaining sinus rhythm for patients with a history of AF.⁶ Rates of recurrent AF were 64% vs. 42%, respectively.

Dronedarone is less effective than amiodarone in maintaining sinus rhythm for patients with AF and increases mortality among patients with recently decompensated or NYHA class III or IV heart failure. The FDA advises against use in these settings in a black box warning. It is however generally well tolerated and does not have the principal iodine-related toxicities of amiodarone. It is contraindicated for patients with sinus bradycardia <50 or significant conduction system disease. Its cost (260 USD per month) is considerably more than that of amiodarone (100 USD per month).⁷ What is the role of this new drug in clinical practice? It has a role for patients with a compelling indication for amiodarone who have a contraindication to its use or who have had important side effects with its use in the past. Despite its apparent safety, due to higher cost and lower efficacy, it should not be a first line antiarrhythmic medication to maintain AF.

Roflumilast

Cigarette smoking is the leading preventable cause of death in the US and most of the developed world. One consequence, chronic obstructive pulmonary disease (COPD), is a progressive, disabling disease that is the fourth leading cause of death in the US.⁸ The GOLD classification is commonly used to stratify severity of disease in patients with COPD (Table 1). Unfortunately, despite current optimal therapy, many patients with stage III or stage IV COPD have disabling symptoms that restrict activity and lifestyle. In addition, no

existing treatment has been shown to slow the expected progression of COPD over time. While tiotropium reduces hospitalizations and the risk of exacerbation, it does not reduce the rate of decline in forced expiratory volume in 1 s (FEV1).⁹ Finally, survival for patients with advanced COPD is poor; the 10-year survival rate for smokers >50 years old with stage III or IV COPD is only 15%.¹⁰ Clearly, there is a need for more effective therapy.

In this context, roflumilast is a novel anti-inflammatory agent that inhibits phosphodiesterase-4 (PDE4). PDE4 causes cytokine release, and recruitment and proliferation of macrophages, neutrophils, and lymphocytes. Roflumilast is an oral PDE4 inhibitor that can be given as a single daily dose. It has the potential to decrease airway inflammation and sputum production,¹¹ and to improve lung function in patients with COPD.

The first large trial to study the impact of roflumilast on clinical outcomes for patients with COPD was a randomized controlled trial (n=1,157) of two different doses of roflumilast versus placebo for 24 weeks.¹² Eligible patients were >40 years old who had a >10 pack-year cigarette history and GOLD stage II–III COPD. Exclusion criteria included asthma, an exacerbation of disease in the previous 4 weeks, and frequent (>8 puffs/day) use of a rescue inhaler. At 24 weeks, there was an improvement in post-bronchodilator FEV1 in both treatment groups as compared to a decline for placebo-treated patients. The differences compared to placebo were 74 cc for roflumilast 250 mcg daily and 97 cc for roflumilast 500 mcg daily. Health-related quality of life, as determined by SGRQ (St. George's respiratory questionnaire)¹³ symptom scores, were significantly improved for both doses of the drug when compared to placebo. In a secondary analysis, the mean number of exacerbations decreased with both doses of roflumilast when compared to placebo (0.75 vs 1.03 vs 1.13, respectively, $p=0.01$). Diarrhea and nausea were the most common drug-related adverse effects, occurring in 7% and 4% of patients, respectively.

Subsequently, Calverley and colleagues reported the results of a study that restricted eligibility to patients (n=1,514) with severe COPD (FEV1<50%) who used the higher dose of roflumilast (500 mcg daily) and followed the patients for 1 year.¹⁴ Post-bronchodilator FEV1 declined during treatment, but to a lesser degree than for placebo treated patients (-35 cc vs -88 cc, $p<0.01$). Symptom scores and rates of exacerbations did not differ between the two groups although exacerbations were fewer among the subset of patients with GOLD class IV COPD (1.01 vs 1.59, $p=0.024$).

Table 1. GOLD Classification for Severity of COPD and Recommended Treatment Strategies

Class	Spirometric criteria		Recommended treatments			
	FEV1*	FEV1/FVC ratio	Short-acting bronchodilator	Long-acting bronchodilator†	Inhaled glucocorticoids	Oxygen if needed
I: Mild	≥80%	<70%	✓			
II: Moderate	50%–80%	<70%	✓	✓		
III: Severe	30%–50%	<70%	✓	✓	✓	
IV: Very severe	<30% or <50% with respiratory failure	<70%	✓	✓	✓	✓

*% predicted; FEV1 Forced expiratory volume in one second, FVC forced vital capacity

†Long-acting inhaled beta-agonist or anticholinergic

Adapted from Global Initiative for Chronic Obstructive Lung Disease: Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease. 2009 Update. Available at: www.goldcopd.com.

In a similarly designed study reported in the *Lancet* in 2009, authors pooled data from two identical trials of patients with COPD and FEV1 <50% predicted who were randomly assigned to roflumilast 500 mcg daily or placebo for 1 year. Post-bronchodilator FEV1 increased by 50 cc in the treatment group compared to a reduction of 4 cc in the placebo group ($p > 0.0001$). Moderate to severe exacerbations occurred less often among patients receiving the active drug (1.14 vs 1.37, $p = 0.0003$). Adverse effects that occurred more commonly for roflumilast users were diarrhea (8% vs 3%), nausea (4% vs 2%), and weight loss (10% vs 3%).

An important clinical question is whether roflumilast performs equally well when combined with other therapies for COPD. Fabbri et al. addressed this question in a study of roflumilast add-on therapy published in the *Lancet* in 2009.¹⁵ In two randomized controlled trials (reported in a single manuscript), patients ($n = 933$) with moderate COPD (FEV1 40%–70% predicted) and a ≥ 10 pack-year cigarette history were randomly assigned, after a 4-week placebo run-in period, to tiotropium plus either placebo or roflumilast, or to salmeterol plus either placebo or roflumilast, for 24 weeks. For each comparison, pre-bronchodilator FEV1 rose significantly for combination treatment as compared to a fall in FEV1 for patients receiving inhaled therapy only. For the tiotropium comparison, the difference was [+65 cc vs -16 cc ($p < 0.0001$)], and for the salmeterol comparison, the difference was [+39 cc vs -10 cc ($p < 0.0001$)]. Symptom scores improved with combination therapy including tiotropium, but not for the roflumilast/salmeterol comparison. Exacerbation rates did not differ for either comparison.

Roflumilast has also shown promise for the treatment of asthma. In a phase 2/3 trial that did not include a placebo arm, roflumilast conferred reduction in symptoms and rescue inhaler use.¹⁶ The magnitude of improvement in FEV1 was greater than that seen when used for the treatment of COPD (400 cc for roflumilast 500 mcg daily for 12 weeks). Clinicians should, however, consider these results to be preliminary.

Roflumilast has now been studied in nearly 7000 patients and has a favorable side effect profile. To date, no significant drug interactions have been reported. It is easy to administer as a single daily oral dose. Patients will become less symptomatic, with the possible exception of roflumilast taken together with salmeterol. It is unknown if patients with mild COPD, who were not included in the studies, would gain similar benefit. Importantly, it is the first drug shown to slow or reverse the expected fall in FEV1 over time. While existing studies do not extend beyond 1 year of treatment, it is possible that roflumilast may have a beneficial effect on long-term mortality; future studies and clinical experience may shed light on this question. In September 2009, the manufacturer filed a new drug application (NDA) for roflumilast with the FDA for the indication of symptomatic COPD. If approved, roflumilast has the potential to be a major advance in the treatment of moderate to severe COPD.

density (BMD) measurement, the relationship between bisphosphonate use and atypical femur fractures, and the duration of treatment with bisphosphonates.

The National Osteoporosis Foundation recommends that patients undergoing treatment for osteoporosis undergo BMD testing every 2 years.¹⁷ In contrast, the North American Menopause Society 2010 guideline recommends checking BMD once, after 2 years of treatment. According to this guideline, if the BMD is stable or improved at 2 years, there is little value in repeating it. Their rationale includes the limited value of BMD testing in predicting effectiveness of treatment and recognition that changes in BMD lag behind therapeutic benefits of bisphosphonates.¹⁸

In 2009, several small case series described patients on bisphosphonates for 5 or more years who developed atypical femur fractures.^{19,20} Hip fractures usually occur below the head of the femur, through the neck of the femur, and between the greater and lesser trochanter. In contrast, these atypical fractures were subtrochanteric, and diaphyseal, through the femur shaft. Subsequently, several larger scale studies have concluded that these atypical fractures are due to osteoporosis itself and not bisphosphonate use. For example, Danish investigators reported results of a cohort study of patients with prior non-hip fractures.²¹ They compared 5,187 patients on alendronate to 10,374 patients who were matched by sex, age, and location of baseline fracture. They found no increase in atypical fractures among patients who were taking alendronate.

Black and colleagues reviewed the hip fracture data from three large randomized bisphosphonate trials: the FIT trial in which patients took alendronate for up to 4.5 years, the FLEX trial, where patients took alendronate for up to 10 years, and the HORIZON-PFT trial where patients took zoledronic acid for up to 3 years.²² A total of 283 fractures occurred among 14,195 women; only 12 of these fractures occurred in the subtrochanteric or diaphyseal femur (2.3 per 10,000 patient-years). The relative hazard of treatment compared with placebo was not statistically significant, though the confidence intervals were wide (Table 2). The authors concluded that subtrochanteric or diaphyseal fractures were rare even in women treated with bisphosphonates for up to 10 years. The accompanying editorial concluded that many more hip fractures are prevented by bisphosphonates than are potentially caused by them.²³

Schwartz and colleagues addressed the question of the optimal duration of alendronate therapy.²⁴ Their analysis of data from the FLEX trial concluded that continuing alendronate for 10 years instead of 5 years reduced non-vertebral fracture risk only for women whose femoral neck T scores, after completing 5 years of treatment, were -2.5 or less (RR=0.50, 95% CI 0.26–0.96). The implication for practice is that it is beneficial to continue bisphosphonates for 10 years only in

NEW GUIDELINES

Osteoporosis

Three challenging issues in the management of patients with osteoporosis are the optimal frequency for bone mineral

Table 2. Relative Hazard of Subtrochanteric or Diaphyseal Fracture Among Patients Receiving Bisphosphonate Therapy Versus Placebo for the Treatment of Osteoporosis

TRIAL	Relative hazard (95% CI)	P value
FIT	1.03 (0.06–16.46)	0.98
FLEX	1.33 (0.12–14.67)	0.82
HORIZON-PFT	1.50 (0.25–9.00)	0.65

Data from *N Engl J Med* 2010;362:1761

patients with persistent osteoporosis by BMD testing after 5 years of treatment.

Aspirin for Primary Prevention of Cardiovascular Disease

Recommendations for aspirin use for primary prevention of cardiovascular disease have evolved since the 2008 American Heart Association recommendations. The guidelines recommended aspirin for men with a 10-year risk of coronary heart disease of $\geq 10\%$ for primary prevention of myocardial infarction (MI), and for women if the benefit of ischemic stroke prevention outweighed the risk of the aspirin.²⁵

In 2009, the US Preventive Services Task Force published a new guideline that recommended aspirin for men aged 45–79 to decrease the risk of MI when the benefit outweighs the potential harm of increase in gastrointestinal (GI) hemorrhage (an “A” recommendation). A new contribution is the calculation of the Framingham 10-year cardiac risk level at which cardiovascular (CV) benefit exceeds GI harms (Table 3). They recommend that women aged 55–79 should take aspirin when the reduction in ischemic stroke risk outweighs the potential harm of increase in GI hemorrhage (an “A” recommendation) (Table 3). They used the Framingham Stroke Risk calculator, [available online at: www.stroke-education.com/calc/risk_calc.do]²⁶ to calculate the 10-year risk of stroke. Factors that increase the risk of GI bleeding include: increasing age, male sex, taking NSAIDs plus aspirin, and history of GI ulcer. Enteric or buffered aspirin does not reduce risk. The optimum aspirin dose is unknown; 81 mg/day is as effective as higher doses, and GI bleeding risk may increase with higher aspirin doses. They found insufficient evidence to recommend aspirin for people ≥ 80 years old (an “I” statement), and did not recommend its use for men younger than 45 years and women younger than 55 years (a “D” recommendation).

The Antithrombotic Trialists’ Collaboration meta-analysis, published later in 2009, cast doubt on the value of aspirin for primary prevention. This study was a meta-analysis of serious vascular events and major bleeding in 6 primary and 16 secondary prevention trials of aspirin vs. control.²⁷ Aspirin for primary prevention was associated with a 12% reduction in serious vascular events due to a reduction in MI. There was no demonstrable effect on stroke or vascular mortality. There was a small but significant increase in bleeding rates: 0.1% vs. 0.07% per year, RR 1.54 (95% CI 1.30–1.82). The authors concluded that aspirin was of uncertain net value for primary prevention and that it was

necessary to weigh the anticipated reduction in occlusive events against the increase in major bleeding complications.

There has also been re-assessment of the role of aspirin for primary prevention of CV events in diabetics. A recent meta-analysis of RCTs from 1966–2008 evaluated six eligible trials with a total of 10,117 participants.²⁸ When compared to placebo, aspirin conferred no reduction in CV events (RR 0.90, 96% CI 0.81–1.00), CV mortality (RR 0.94, 95% CI 0.72–1.23), or all-cause mortality (RR 0.93, 95% CI 0.82–1.05). When stratified by gender, men had a statistically significant decrease in rates of MI (RR 0.57, 95% CI 0.34–0.94), whereas women did not benefit (RR 1.08, 95% CI 0.71–1.65).

The 2010 American Diabetes Association guidelines no longer recommend routine aspirin use in diabetics. Their current recommendation is to consider aspirin for primary prevention in diabetic patients who are at increased cardiovascular risk (10 year risk $> 10\%$). This includes men > 50 years old and women > 60 years old who have at least one additional risk factor.²⁹

Vitamin D

In the US, estimates are that 36% of healthy young adults and 57% of general medicine inpatients have vitamin D deficiency.³⁰ Definitions of vitamin D levels are: sufficient: total 25(OH)D > 30 ng/ml, insufficient: 20–30 ng/ml, and deficient: < 20 ng/ml. Causes of vitamin D deficiency include inadequate sun exposure and inadequate food sources. Risk factors include dark skin, chronic renal or liver disease, medications including anticonvulsants and steroids, advanced age, housebound or nursing home status, and obesity.

The prevalence of vitamin D deficiency is increasing. For example, a comparison of 25(OH)D levels from the NHANES 1988–1994 and 2001–2004 data show a marked decrease in mean vitamin D levels in the 2001–2004 cohort.³¹ The increasing prevalence of obesity may contribute to the rising rates of vitamin D deficiency. BMI correlates inversely with 25(OH)D levels; vitamin D deficiency is strongly associated with subcutaneous and visceral adiposity.³²

Vitamin D deficiency is the most common basis for secondary osteoporosis. Vitamin D supplementation reduces the risk of fracture. The Women’s Health Initiative, a randomized controlled trial of 36,282 women ages 50–69 assigned to calcium 100 mg/day plus vitamin D 400 IU/day or placebo, evaluated bone mineral density (BMD) and hip fractures.³³ Hip BMD was 1.06% higher in the calcium-vitamin D group. Compliant patients (defined as those who took more than 80% of medicine) had a significant decrease in hip fracture (HR 0.71, 95% CI 0.52–0.97). A meta-analysis of seven RCTs in 9,820 elderly subjects (mean age 79) showed that those receiving higher doses of vitamin D supplementation (700–800 IU/day) had lower rates of hip (RR 0.74, 95% CI 0.61–0.88) and vertebral (RR 0.77, 95% CI 0.68–0.87) fracture.³⁴

Several studies have found that vitamin D supplementation decreases the risk of falls. In a meta-analysis of 5 RCTs of vitamin D involving 1,237 older subjects (mean age 60), vitamin D use reduced the risk of falls by 22% compared with patients receiving calcium or placebo (OR 0.78, 95% CI 0.64–0.92).³⁵ The number needed to treat (NNT) to prevent one fall was 15 patients. In a subsequent report, 96 elderly women with poststroke hemiplegia were randomly assigned to treatment

Table 3. Risk Level at Which Beneficial Effects of Aspirin Exceed Risks of Major Bleeding

Age	Men: 10-year risk of myocardial infarction	Women: 10-year risk of stroke
45–59 years	$\geq 4\%$	
55–59 years		$\geq 3\%$
60–69 years	$\geq 9\%$	$\geq 8\%$
70–79 years	$\geq 12\%$	$\geq 11\%$

Adapted with permission from *Ann Intern Med* 2009;150:396

with 1,000 IU vitamin D or placebo for 2 years. Treatment with vitamin D conferred a 59% decrease in falls and improvement in muscle strength.³⁶ Finally, in a 1-year RCT of 302 women aged 70–90 with 25(OH)D levels less than 24 and a history of falling, treatment with vitamin D2 1,000 IU/day significantly decreased the risk of falls compared to placebo (OR 0.61, 95% CI 0.37–0.99).³⁷

There is conflicting evidence about the relationship between vitamin D and cancer risk. Several observational studies have reported that high vitamin D levels are associated with decreased cancer risk. However, RCTs of vitamin D supplementation have shown no reduction in the risk of cancer. For example, in the Women's Health Initiative RCT, 36,282 women were randomly assigned to 1,000 mg calcium and 400 IU vitamin D3 or placebo for an average of 7 years.³³ At the completion of the trial, there was no difference in the incidence of colorectal cancer³⁸ or invasive breast cancer.

Observational studies have demonstrated associations between low vitamin D levels and increased all-cause and cardiovascular mortality.³⁹ A recent meta-analysis of randomized controlled trials reported lower all-cause mortality rates among patients receiving vitamin D supplementation (RR 0.92, 95% CI 0.86–0.99).⁴⁰ However, mortality was not a primary endpoint in any of these trials; a statistically significant benefit was not observed in any of the individual studies. Still, the random allocation of patients in these studies diminishes concerns about residual confounding. Future research should include large-scale population-based RCTs that evaluate mortality as the primary endpoint. Prevention of vitamin D deficiency is part of optimal primary care practice. As testing for vitamin D deficiency can be expensive, a reasonable approach is to provide adequate supplementation with 1,000 IU of vitamin D3 daily for all patients.

Conflicts of interest: Dr. Smetana has served as a consultant to Anvita Health. Dr. Sillman reports no conflicts.

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REFERENCES

- Drugs @ FDA. FDA approved drug products. 2010. Accessed June 21, 2010. Available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>.
- Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370–5.
- Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–33.
- Singh BN, Connolly SJ, Crijns HJ, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med*. 2007;357:987–99.
- Kober L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med*. 2008;358:2678–87.
- US Food and Drug Administration. Multaq (dronedarone): Briefing Document. In: Advisory committee meeting of the cardiovascular and renal drugs division of the US Food and Drug Administration March 18, 2009. p. 1–144. Accessed June 26, 2010. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM134981.pdf>.
- Red Book. February 2010 Update. Montvale NJ.: PDR Network
- Center for Disease Control. Leading causes of death in 2006. Accessed July 2, 2010. Available at: <http://www.cdc.gov/nchs/fastats/lcod.htm>.
- Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:1543–54.
- Shavelle RM, Paculdo DR, Kush SJ, Mannino DM, Strauss DJ. Life expectancy and years of life lost in chronic obstructive pulmonary disease: findings from the NHANES III Follow-up Study. *Int J Chron Obstruct Pulmon Dis*. 2009;4:137–48.
- Grootendorst DC, Gauw SA, Verhoosel RM, et al. Reduction in sputum neutrophil and eosinophil numbers by the PDE4 inhibitor roflumilast in patients with COPD. *Thorax*. 2007;62:1081–7.
- Rabe KF, Bateman ED, O'Donnell D, Witte S, Bredenbroeker D, Bethke TD. Roflumilast—an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet*. 2005;366:563–71.
- Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's respiratory questionnaire. *Am Rev Respir Dis*. 1992;145:1321–7.
- Calverley PM, Sanchez-Toril F, McIvor A, Teichmann P, Bredenbroeker D, Fabbri LM. Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;176:154–61.
- Fabbri LM, Calverley PM, Izquierdo-Alonso JL, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. *Lancet*. 2009;374:695–703.
- Bateman ED, Izquierdo JL, Harnest U, et al. Efficacy and safety of roflumilast in the treatment of asthma. *Ann Allergy Asthma Immunol*. 2006;96:679–86.
- National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Washington DC: National Osteoporosis Foundation; 2010.
- Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause*. 2010;17:25–54; quiz 5–6.
- Capeci CM, Tejwani NC. Bilateral low-energy simultaneous or sequential femoral fractures in patients on long-term alendronate therapy. *J Bone Joint Surg Am*. 2009;91:2556–61.
- Lenart BA, Neviaser AS, Lyman S, et al. Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. *Osteoporos Int*. 2009;20:1353–62.
- Abrahamsen B, Eiken P, Eastell R. Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. *J Bone Miner Res*. 2009;24:1095–102.
- Black DM, Kelly MP, Genant HK, et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. *N Engl J Med*. 2010;362:1761–71.
- Shane E. Evolving data about subtrochanteric fractures and bisphosphonates. *N Engl J Med*. 2010;362:1825–7.
- Schwartz AV, Bauer DC, Cummings SR, et al. Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: the FLEX trial. *J Bone Miner Res*. 2010;25:976–82.
- Mosca L. Aspirin chemoprevention: one size does not fit all. *Circulation*. 2008;117:2844–6.
- Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1991;22:312–8.
- Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373:1849–60.
- De Berardis G, Sacco M, Strippoli GF, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. *BMJ*. 2009;339:b4531.
- Executive summary: Standards of medical care in diabetes—2010. *Diabetes Care*. 2010;33 Suppl 1:S4–10.
- Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357:266–81.
- Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. *Arch Intern Med*. 2009;169:626–32.
- Cheng S, Massaro JM, Fox CS, et al. Adiposity, cardiometabolic risk, and vitamin D status: the Framingham heart study. *Diabetes*. 2010;59:242–8.

33. **Chlebowski RT, Johnson KC, Kooperberg C, et al.** Calcium plus vitamin D supplementation and the risk of breast cancer. *J Natl Cancer Inst.* 2008;100:1581–91.
34. **Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B.** Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA.* 2005;293:2257–64.
35. **Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al.** Effect of Vitamin D on falls: a meta-analysis. *JAMA.* 2004;291:1999–2006.
36. **Sato Y, Iwamoto J, Kanoko T, Satoh K.** Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. *Cerebrovasc Dis.* 2005;20:187–92.
37. **Prince RL, Austin N, Devine A, Dick IM, Bruce D, Zhu K.** Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. *Arch Intern Med.* 2008;168:103–8.
38. **Wactawski-Wende J, Kotchen JM, Anderson GL, et al.** Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med.* 2006;354:684–96.
39. **Melamed ML, Michos ED, Post W, Astor B.** 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med.* 2008;168:1629–37.
40. **Autier P, Gandini S.** Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med.* 2007;167:1730–7.