Published in final edited form as:

Am J Geriatr Pharmacother. 2012 August ; 10(4): 258–263. doi:10.1016/j.amjopharm.2012.05.003.

A Year in Review: New Drugs for Older Adults in 2011

Joseph P. Vande Griend, PharmD¹, Zachary A. Marcum, PharmD, MS², and Sunny A. Linnebur, PharmD¹

¹Department of Clinical Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Aurora, Colorado

²Department of Medicine, Division of Geriatric Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

Abstract

Background—New drugs approved by the Food and Drug Administration (FDA) may offer tremendous clinical advances by providing health care providers with new treatment strategies. However, additional care must be taken for safe and effective use of these new agents by older adults.

Objective—Our objective was to identify FDA-approved medications in 2011 most likely to be prescribed to older adults, and to describe medication characteristics that may require special attention in this population.

Methods—The FDA Web site was reviewed for new drug approvals from January through December 2011. Approved labeling for each drug was obtained from the manufacturer's Web site and PubMed was searched for primary literature published between 1967 and 2012.

Results—Rivaroxaban, an oral factor Xa inhibitor, is approved for once-daily use in treatment of nonvalvular atrial fibrillation and deep vein thrombosis prophylaxis after replacement of a hip or knee. Drug interactions and renal function must be considered when prescribing this drug to older adults. Fidaxomicin is an oral anti-infective approved for the treatment of *Clostridium difficile*-associated diarrhea. It has minimal oral absorption or side effects, no relevant drug interactions, but a very high cost. It is a treatment option after failure of oral metronidazole and oral vancomycin. Roflumilast is a selective inhibitor of phosphodiesterase 4 and is approved to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD and a history of exacerbations. It is recommended as a second or alternative choice combined with a long-acting bronchodilator in patients at high risk for hospitalization. Indacaterol is an inhaled long-acting β -agonist approved for COPD maintenance. It is administered once daily, which may improve adherence in older adults compared with currently available twice-daily agents.

© 2012 Elsevier HS Journals, Inc. All rights reserved.

Address correspondence to: Joseph P. Vande Griend, PharmD, Department of Clinical Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Mail Stop C238, 12850 E. Montview Blvd, Room V20-2127, Aurora, CO 80045. joseph.vandegriend@ucdenver.edu.

This work was presented in part at the Pharmacotherapy Update Symposium at the annual American Geriatric Society Meeting, Seattle, Washington, May 6, 2012.

Conflicts of Interest: The authors have indicated that they have no other conflicts of interest regarding the content of this article.

Conclusions—Four new drugs approved in 2011 applicable to the geriatric population are presented. Clinicians must consider the available evidence, cost, drug–drug interactions, renal function, pharmacokinetic/pharmacodynamic differences, and patient preferences when considering prescribing these agents to older adults.

Keywords

fidaxomicin; indacaterol; rivaroxaban; roflumilast

Introduction

The Food and Drug Administration (FDA) evaluates and approves new molecular entities each year, several of which are applicable to treatment regimens prescribed to older adults. These new drugs may offer tremendous clinical advances by providing health care providers with new treatment strategies, but additional care must be taken for safe and effective use of these new agents. This is especially true when prescribing for older adults who are often underrepresented in clinical trials.¹ Older adults with multiple comorbidities, those with decreased renal function, and those taking multiple medications often do not meet inclusion or exclusion criteria for clinical trials.¹ Older adults may also be more vulnerable to the high cost of new medications, drug–drug interactions, and pharmacokinetic differences affecting drug dosing and elimination as well as pharmacodynamic changes.¹ Along with patient preference, these aspects must be weighed when considering prescribing a new drug to an older adult. The objective of this review is to identify medications approved by the FDA in 2011 that are likely to be used by older adults, and to describe drug-specific characteristics that may require special attention in this population.

Methods

The FDA Web site was reviewed for new drug approvals from January through December 2011. Drugs were included in this review according to the following criteria: (1) they had potential to be prescribed in the general population of older adults, and (2) they were expected to have a significant influence on the care of older adults. For drugs chosen, approved labeling was obtained from the manufacturer and PubMed was searched for relevant primary literature published between 1967 and 2012.

Discussion

Thirty new molecular entities were approved by the FDA during 2011. Rivaroxaban,^{*} fidaxomicin,[†] roflu-milast,[‡] and indacaterol[§] were chosen as agents expected to have a significant influence on the care of older adults.

*Trademark: Xarelto® (Janssen Pharmaceuticals Inc, Titusville, New Jersey).

†Trademark: Dificid® (Optimer Pharmaceuticals, Inc, San Diego, California).

‡Trademark: Daliresp® (Forest Pharmaceuticals, Inc, St Louis, Missouri).

§Trademark: Arcapta™ (Novartis Corp, East Hanover, New Jersey).

Rivaroxaban

Mechanism/Indications—Rivaroxaban is a once daily oral factor Xa inhibitor. It was approved for deep vein thrombosis prophylaxis after hip and knee replacement in July 2011 and to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation in November 2011.²

Dosing—For deep vein thrombosis prophylaxis, the approved dosing is 10 mg orally once daily starting at least 6 to 10 hours after surgery and once hemostasis has been established (treatment duration 35 days for hip replacement, 12 days for knee replacement). For this indication, rivaroxaban is not recommended in patients with creatinine clearance (CrCl) <30 mL/min. For nonvalvular atrial fibrillation, the approved dosing is 20 mg daily (CrCl >50 mL/min) or 15 mg daily (CrCl = 15 to 50 mL/min). Use should be avoided in patients with CrCl <15 mL/min.

Pharmacokinetics—Oral absorption of rivaroxaban is dose-dependent. The 10-mg dose can be taken without regard to food, but the 15-mg and 20-mg doses should be taken with the evening meal to optimize absorption. Two-thirds of rivaroxaban is metabolized hepatically, primarily through the cytochrome P-450 3A4 system (CYP3A4); the remaining one-third is not metabolized by the liver, but is eliminated renally as unchanged drug.² Because both elimination pathways can be affected by increasing age, this drug has a longer half-life in elderly patients (11–13 hours) compared with patients aged 20 to 45 years (5–9 hours).² Despite the difference in half-life, there is no dose adjustment recommended based on age alone. Drugs that inhibit or induce *both* the CYP3A4 and the p-glycoprotein (Pgp) system have the potential to cause clinically relevant drug interactions with rivaroxaban. Pgp is a transport protein that aids in the movement of drugs across membranes in the body. In the gastrointestinal tract, inhibition and induction of Pgp can result in increased and decreased rivaroxaban concentrations in the body, respectively. Drugs that are strong inhibitors (ie, ketoconazole, itraconazole, lopina-vir/ritonavir, ritonavir, indinavir/ritonavir, and conivap-tan) and strong inducers (ie, rifampin, carbamazepine, phenytoin, phenobarbital, and St John's wort) of both CYP3A4 and Pgp should be avoided in combination with rivaroxaban. In a patient with renal impairment, the concomitant use of rivaroxaban with a drug that is both a weak-moderate CYP3A4 and a Pgp inhibitor should be done with caution because drug elimination is decreased by 2 pathways. This concern is especially relevant in older adults who may already have a longer drug half-life given age-related changes in hepatic and renal clearance. In these patients, rivaroxaban should only be used if the benefits outweigh the potential increased risk of bleeding.²

Evidence from Clinical Trials—In older adults, rivaroxaban will most likely be prescribed chronically for the reduction of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Rivaroxaban received FDA approval for this indication based on the results of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation, a noninferiority trial comparing rivaroxaban 15 mg (CrCl 30–49 mL/min) or rivaroxaban 20 mg (CrCl ≥ 50 mL/min) with warfarin adjusted to an international normalized ratio between 2 and 3 in patients at moderate to high risk.³ Patients included had

a history of stroke, transient ischemic attack, or systemic embolism or at least 2 of the following risk factors: heart failure or a left ventricular ejection fraction of $\leq 35\%$, hypertension, age ≥ 75 years, or the presence of diabetes mellitus. The mean CHADS₂ score of patients was approximately 3.5, which indicates a high risk of stroke. Patients with CrCl <30 mL/min, liver disease, treatment with a strong CYP3A4 inhibitor/inducer, concomitant use of aspirin >100 mg/day, combination aspirin plus thienopyridine use, a severe heart valve disorder, or a high bleeding risk were excluded. More than 14,000 patients with a median age of 73 years (interquartile range = 65–78 years) participated. Approximately 55% had a previous stroke, transient ischemic attack, or systemic embolism, and 36% were taking aspirin. After a median duration of 590 days, rivaroxaban was shown to be noninferior for the primary efficacy endpoint of stroke and systemic embolism (hazard ratio in the rivaroxaban group = 0.79; 95% CI, 0.66–0.96; $P < 0.001$ for noninferiority). For the pre-specified safety endpoint of clinically relevant major and no-major bleeding, no difference between rivaroxaban and warfarin was observed (hazard ratio in the rivaroxaban group = 1.03; 95% CI, 0.96–1.11; $P = 0.44$).

Clinical Considerations/Cost—Rivaroxaban is the first oral alternative to warfarin approved since dabigatran^{||} was approved in 2010. Clinicians will likely consider both agents when evaluating oral alternatives to warfarin, although rivaroxaban was not discussed in detail in the most recent antithrombotic guidelines.⁴ Several differences between the 2 agents exist. Dabigatran is a direct thrombin inhibitor, it is dosed twice daily, and its elimination is almost entirely dependent on the kidneys. Hepatic interactions are not relevant, although P-gp interactions may still play a role with dabigatran use. In contrast to dabigatran, rivaroxaban was studied in a population with a higher CHADS₂ score (3.5 vs 2.1) in its pivotal Phase III trial, the drug does not have storage restrictions, and dyspepsia has not been noted with its use. Once-daily dosing with rivaroxaban may improve adherence in older adults compared with dabigatran. Finally, insurance coverage will need to be considered when choosing between dabigatran and rivaroxaban. The average wholesale price of the drug is \$243.

Fidaxomicin

Mechanism/Indication—Fidaxomicin is bactericidal against *C. difficile*, and thought to inhibit bacterial protein synthesis binding to bacterial RNA polymerase.⁵ It was approved by the FDA in May 2011 for the treatment of *C. difficile*-associated diarrhea in patients aged 18 years.

Dosing/Pharmacokinetics—Fidaxomicin is given at a dose of 200 mg twice daily for 10 days. The drug has minimal oral absorption; thus, there are no clinically relevant drug interactions. Minimal absorption also maximizes the concentration of drug at the site of action in the gastrointestinal tract, and 92% of the parent drug and active metabolite are recovered in the stool. No dose adjustments are needed for age.

^{||}Trademark: Pradaxa® (Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT).

Evidence from Clinical Trials—Fidaxomicin was compared with oral vancomycin in a noninferiority trial.⁶ Patients (n = 629) with a diagnosis of *C. difficile* infection were randomized to either fidaxomicin 200 mg twice daily or oral vancomycin 125 mg 4 times daily, each for 10 days. Those included had mild (25%), moderate (37%), and severe (39%) disease and approximately 60% were inpatients. Fidaxomicin was noninferior to vancomycin for the primary outcome of clinical cure, defined as a resolution of symptoms and no need for further therapy as of the second day after therapy ended. Fidaxomicin reduced the rate of recurrence, defined as diarrhea with a positive stool culture requiring retreatment within 4 weeks, compared with vancomycin (15.4% vs 25.3%; $P = 0.005$). There was no difference in recurrence among the hypervirulent strain (NAP1/ BI/027), but there was a significant difference in those with the nonhypervirulent strain (7.8% vs 25.5%; $P < 0.001$) favoring fidaxomicin. Side effects of fidaxomicin are typically gastrointestinal in nature and include nausea (11%), vomiting (7%), and abdominal pain (6%).

Clinical Considerations/Cost—Fidaxomicin can be considered after first- and second-line failure with oral metronidazole and/or oral vancomycin, depending on disease severity. Depending on insurance coverage, fidaxomicin may be cost-prohibitive for some elderly patients. The average wholesale price for a 10-day course of fidaxomicin is estimated to cost ~\$3360, compared with an average wholesale price of \$1273 for oral vancomycin 125 mg 4 times daily. A 10-day course of metronidazole 250 mg 4 times daily is expected to be significantly cheaper.

Roflumilast

Mechanism/Indication—Both roflumilast and its active metabolite, roflumilast N-oxide, are selective inhibitors of phosphodiesterase 4, an enzyme that metabolizes cyclic adenosine monophosphate and is widely distributed in the lungs. Increased cyclic adenosine monophosphate (via inhibition of phosphodiesterase 4) in the lungs is thought to inhibit inflammation.^{7,8} This is a novel mechanism for treatment of chronic obstructive pulmonary disease (COPD). Roflumilast was approved by the FDA in February 2011 to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.⁸

Dosing/Pharmacokinetics—Roflumilast is given at a dose of 500 μ g daily. The drug is contraindicated in moderate to severe liver impairment (Child-Pugh grades B and C), and dosage adjustment for renal impairment is not necessary. Strong CYP3A4 enzyme inducers (eg, rifampicin, phenobarbital, carbamazepine, and phenytoin) decrease systemic exposure to roflumilast, potentially reducing its effectiveness, and are therefore not recommended for concurrent use.⁸ Inhibitors of CYP3A4 and inhibitors of both CYP3A4 and cytochrome P450 1A2 (eg, erythromycin, ketoconazole, fluvoxamine, and cimetidine) may increase roflumilast systemic exposure, potentially resulting in increased adverse reactions, and therefore should be used with caution.

Evidence from Clinical Trials—Roflumilast 500 μ g daily has been compared with placebo in >3000 patients (mean age = 64 years, 75% male) with severe (62%) and very severe (29%) COPD.⁹ Roflumilast significantly reduced the primary endpoint of moderate

(ie, requiring oral or parenteral corticosteroids) plus severe (ie, hospital admission or death) COPD exacerbation compared with placebo (relative risk = 0.83; 95% CI, 0.75–0.92; $P = 0.0003$). The primary endpoint was driven by differences in the rate of moderate COPD exacerbation (relative risk = 0.83; 95% CI, 0.75–0.92; $P = 0.0007$) because there was no difference in the rate of severe COPD exacerbation. Overall, the absolute risk reduction for the primary end-point was 6.2%, which correlates to a number needed to treat of 16 to prevent 1 moderate or severe COPD exacerbation. Treatment with roflumilast has been associated with an increase in psychiatric adverse events, including insomnia, anxiety, and depression. These occurred more than placebo, but at a low frequency (2.4%, 1.4%, and 1.2%, respectively). Weight loss of 5% to 10% of body weight was reported in 20% of patients receiving roflumilast compared with 7% of patients who received placebo in 2 placebo-controlled clinical trials of 1 year duration in which weight was prospectively assessed.⁸ In all controlled clinical trials, approximately 2500 patients with COPD aged 65 years or older ($n = 471$ aged >75 years) have been exposed to roflumilast for up to 12 months. No differences in safety or efficacy in older patients compared with younger patients have been noted.⁸

Clinical Considerations/Cost—The Global Initiative for Chronic Obstructive Lung Disease Guidelines 2011 state that “roflumilast may be useful to reduce exacerbations in patients with $FEV_1 < 50\%$ predicted, chronic bronchitis, and frequent exacerbations.”¹⁰ They further recommend roflumilast as a second and alternative choice in patients with Stage C or Stage D COPD (both stages indicate high risk for exacerbation) in combination with a long-acting bronchodilator. It is important to note that roflumilast has not been studied in comparison with or as add-on therapy to inhaled corticosteroids. Because both inhaled corticosteroids and roflumilast are thought to reduce lung inflammation, it is not known if it will provide benefit when compared with or added to inhaled corticosteroids. The average wholesale cost of this drug is not yet known, but estimated to be around \$200/month.

Indacaterol

Mechanism/Indication—Indacaterol is a novel, once-daily long-acting β -agonist (LABA). It was approved by the FDA in July 2011 for maintenance therapy in COPD.¹¹

Dosing/Pharmacokinetics—The approved dose of indacaterol in the United States is 75 μ g inhaled via a proprietary inhaler device. The 2 other currently available LABA therapies (ie, formoterol and salmeterol) are both dosed twice daily. No dose adjustment is needed for age, renal impairment, or hepatic impairment. Drug interactions are anticipated to be minimal with this drug.

Evidence from Clinical Trials—Indacaterol has shown improvement in forced expiratory volume in 1 second (FEV_1) compared with placebo, but no data exist to show that indacaterol at a dose of 75 μ g reduces COPD exacerbation compared with placebo. Side effects occurring at least 2% of the time with indacaterol and greater than placebo include cough, nasopharyngeal pain, nasopharyngitis, headache, and nausea.¹¹ Tachycardia, tremor, nervousness, and hypertension may also occur given the mechanism of action, and postinhalation cough has occurred in 24% of patients. A systematic review evaluated the

efficacy and safety of indacaterol in comparison with other long-acting bronchodilators.¹² The review included 5 trials and a total of 5920 patients. All trials were multicenter, randomized, and parallel-group designs. Two trials evaluated indacaterol with tiotropium; both were 12 weeks in duration.^{13,14} No difference in mean trough FEV₁ was noted between the 2 agents. Patients treated with indacaterol had reduced rescue inhalation (0.57 fewer puffs per day; $P < 0.0001$) compared with tiotropium, but it is unclear if this is clinically relevant. No differences in the rate of COPD exacerbation, study withdrawal, adverse event, serious adverse event, or all-cause mortality were noted. Two trials compared indacaterol with salmeterol (12 weeks and 26 weeks),^{15,16} and 1 trial compared indacaterol with formoterol (52 weeks).¹⁷ Indacaterol had a higher mean trough FEV₁ of 70 mL compared with twice-daily LABA therapy from the 3 included trials ($P < 0.0001$).^{15–17} Patients treated with indacaterol had reduced rescue inhalation (0.22 fewer puffs per day; $P < 0.0001$) compared with twice-daily LABA therapy, but again, it is unclear if this is clinically relevant.^{15–17} No differences in the rate of COPD exacerbation, study withdrawal, adverse event, serious adverse event, or all-cause mortality were noted.

Clinical Considerations/Cost—Indacaterol can be considered as an alternative to the other long-acting bronchodilators (ie, tiotropium, salmeterol, and formoterol). Unlike available twice-daily LABA therapy, it is not available in combination with an inhaled corticosteroid (eg, salmeterol/fluticasone or formoterol/budesonide). Similar to tiotropium, indacaterol is a once-daily product; however, tiotropium has been shown to reduce COPD exacerbations and related hospitalizations.¹⁰ Elderly patients with difficulty adhering to twice-daily LABA therapy may benefit from once-daily indacaterol. Formulary coverage for indacaterol may play a role in the choice between indacaterol and twice-daily LABA therapy. The average wholesale price is \$197 for a 1-month supply, which is similar to once-daily tiotropium (\$262), and the twice-daily LABAs (ie, salmeterol [\$181] and formoterol [\$176]).

Conclusion

Rivaroxaban, fidaxomicin, roflumilast, and indacaterol will likely be prescribed to and have a significant influence on the care of older adults. Rivaroxaban is approved for once-daily use in treatment of atrial fibrillation and for deep vein thrombosis prophylaxis after hip and knee replacement. Both drug interactions and renal function must be considered when prescribing this drug to older adults. Fidaxomicin is approved for *C. difficile*-associated diarrhea. It has minimal oral absorption or side effects with no relevant drug interactions, has demonstrated efficacy compared with oral vancomycin, but has a very high cost. It should be considered as a treatment option after failure with oral metronidazole and/or oral vancomycin. Roflumilast demonstrated modest benefit in reducing the risk of COPD exacerbations in patients with severe COPD and history of exacerbations. It is recommended as a second or alternative choice combined with a long-acting bronchodilator for patients at high risk for hospitalization. Indacaterol is an inhaled LABA approved as COPD maintenance therapy. It is dosed once daily, which may improve adherence in older adults when compared with currently available twice-daily agents.

Acknowledgments

Dr. Vande Griend conducted the literature search and drafted the initial manuscript. Drs. Marcum and Lin-nebur added substantial contributions to the literature search and provided key contributions to the development of this manuscript.

This work was supported in part by a National Institute on Aging grant (No. P30AG024827). The sponsor had no role or influence in matters related to the research design, methods, data collection, interpretation of data, or in the writing of the manuscript.

References

1. Hajjar, E.; Starner, CI.; Gray, SL., et al. Geriatrics. In: Dipro, JT.; Talbert, RL.; Yee, GC., editors. Pharmacotherapy: A Pathophysiologic Approach. 8th. New York, NY: McGraw-Hill; 2011. p. 135-145.
2. Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2011.
3. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011; 365:883–891. [PubMed: 21830957]
4. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012; 141:e531S–e575S. [PubMed: 22315271]
5. Hardesty JS, Juang P. Fidaxomicin: a macrocyclic antibiotic for the treatment of *Clostridium difficile* infection. *Pharmacotherapy*. 2011; 31:877–886. [PubMed: 21923589]
6. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med*. 2011; 364:422–431. [PubMed: 21288078]
7. Rabe KF. Update on roflumilast, a phosphodiesterase 4 inhibitor for the treatment of chronic obstructive pulmonary disease. *Br J Pharmacol*. 2011; 163:53–67. [PubMed: 21232047]
8. Daliresp [package insert]. St Louis, Mo: Forest Pharmaceuticals, Inc; 2011.
9. Calverley PM, Rabe KF, Goehring UM, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. 2009; 374:685–694. [PubMed: 19716960]
10. [Accessed April 30, 2012] GOLD - the Global Initiative for Chronic Obstructive Lung Disease. <http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html>
11. Arcapta. East Hanover, NJ: Novartis Corp; 2011. package insert
12. Rodrigo GJ, Neffen H. Comparison of indacaterol with tiotropium or twice-daily long-acting beta-agonists for stable copd: a systematic review. *Chest*. 2012 Mar 1. Epub ahead of print.
13. Buhl R, Dunn LJ, Disdier C, et al. Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. *Eur Respir J*. 2011; 38:797–803. [PubMed: 21622587]
14. Donohue JF, Fogarty C, Lotvall J, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: in-dacaterol versus tiotropium. *Am J Respir Crit Care Med*. 2010; 182:155–162. [PubMed: 20463178]
15. Korn S, Kerwin E, Atis S, et al. Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: a 12-week study. *Respir Med*. 2011; 105:719–726. [PubMed: 21367594]
16. Kornmann O, Dahl R, Centanni S, et al. Once-daily in-dacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. *Eur Respir J*. 2011; 37:273–279. [PubMed: 20693243]
17. Dahl R, Chung KF, Buhl R, et al. Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. *Thorax*. 2010; 65:473–479. [PubMed: 20522841]