UPDATE

Update in New Medications for Primary Care

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Each year, the FDA approves dozens of new drugs for use in clinical practice. Clinicians must wade through a staggering amount of evidence to determine which drugs will be important new additions to their practice. Many of the new drugs relate to specialty practices, such as chemotherapeutic agents and immune-based therapies. A fraction of the newly approved drugs are potentially relevant for primary care clinicians. Most of these drugs are "me too" drugs that are a new drug within an existing class of medications. For example, the FDA may approve a new beta-blocker or a new proton-pump inhibitor. When these types of new drugs are as effective and safe as existing drugs, they are welcome primarily when their cost to patients and health plans is lower than that of currently available drugs.

However, a small number of drugs each year are novel and relevant for primary care practice. These are drugs that work through a completely new mechanism compared to existing therapies and have the potential to represent an addition to our pharmacologic armamentarium. It is challenging for busy clinicians to determine which new drugs meet this requirement and to receive balanced information regarding efficacy, safety, side effects, and cost of these new medications. In addition, each year, new practice guidelines and systematic reviews provide guidance regarding optimal use and sequence of existing medications for common clinical problems in primary care. In this paper, we provide a balanced presentation of some of the most important new drugs in primary care, followed by important updates in pharmacologic management of common conditions seen in primary care.

In preparation of the New Drugs section of this paper, we reviewed the FDA database of new drugs[1] approved from January 1, 2006 through March 1, 2008. We excluded drugs that were (1) used exclusively in inpatient settings, (2) parenteral agents, (3) prescribed only by subspecialty providers, or (4) new formulations or combinations of existing medications. From the remaining drugs, we identified those that work by a novel mechanism and represent the first drug in a new class of medications. From this list, we selected those drugs that, in our opinion, had the most relevance and potential to change primary care practice. For the update in Management of Common Conditions section of this paper, we reviewed the following medical journals from January 1, 2006 through April 7, 2008: New England Journal of Medicine, Annals of Internal Medicine, ACP Journal Club, JAMA, Journal Watch, and Hypertension. We identified new practice guidelines and systemic reviews on the pharmacologic management of common and important medical problems managed in the office by general internists and offer our own recommendations for pharmacologic management of these conditions.

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NEW DRUGS

Varenicline

Cigarette smoking is the leading cause of preventible death in the United States and accounts for more than 5 million deaths per year worldwide.[2] Existing pharmacologic treatment strategies, including bupropion and nicotine products, help only a minority of patients. In this context, varenicline is a novel drug. The FDA approved varenicline on May 10, 2006. Nicotine effects on the brain are mediated by specific acetylcholine receptors. Varenicline binds to the $\alpha 4\beta 2$ receptor in the brain where it functions as an agonist and partial antagonist. Theoretically, varenicline could potentially reduce both craving and the reward from nicotine use.

The FDA approved varenicline primarily on the basis of unpublished data from five trials, three of which were subsequently published in JAMA on July 5, 2006: two nearly identical trials of 12 weeks of varenicline 1 mg twice daily versus bupropion or placebo[3,4] and a third trial that examined the benefit of extending therapy to 24 weeks.[5] The investigators determined abstinence by self report and exhaled carbon monoxide measurements. Among a long list of exclusion criteria, important exclusions included patients with a history of alcohol or drug abuse or dependence, those receiving treatment for major depression in the previous 12 months, and those with a history of or current bipolar disorder.

Using the first trial as an example,[4] continuous abstinence rates were significantly higher for patients receiving varenicline than for bupropion or placebo users at each week of the 52-week trial (Fig. 1). Point prevalence abstinence rates for varenicline users were 50% at 12 weeks (completion of treatment phase) and 31% at 52 weeks. Comparable rates for bupropion users were 36% and 23%, and for placebo users 21% and 17%, respectively. In the treatment extension trial, authors randomly assigned patients who successfully quit at 12 weeks to an additional 12 weeks of varenicline or placebo.[5] The additional 12 weeks of varenicline therapy provided a statistically significant, but clinically small additional benefit (continuous abstinence 44% vs 37%, p=0.02).

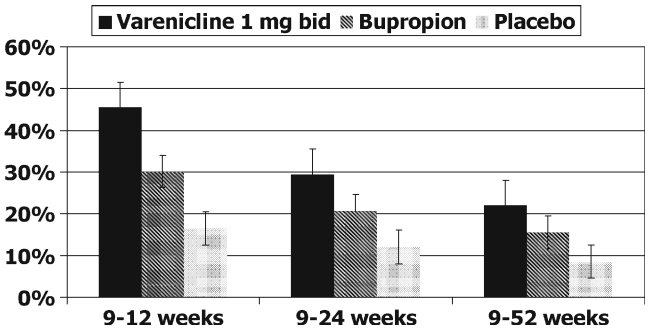

Figure 1. Continuous smoking abstinence rates for varenicline versus bupropion and placebo. Continuous smoking abstinence represents no cigarette smoking at any time during the defined interval. Data from Jorenby DE, Hays JT, Rigotti NA, et al. *JAMA.* 2006;296:56–63.

Since FDA approval, a study of 12 weeks of varenicline versus 10 weeks of a nicotine patch (n=746) reported higher 12-week continuous abstinence [56% vs 43%, OR 1.70 (CI 1.26–2.28)] and a trend towards higher continuous abstinence rates at 52 weeks [26% vs 20%, OR 1.40 (CI 0.99–1.99)] among patients randomly assigned to varenicline.[6]

In the two trials of 12 weeks of varenicline vs. bupropion, pooled adverse effects that were substantially more common among varenicline users than placebo users included nausea (29% vs 9%), constipation (7% vs 3%), flatulence (6% vs 3%), and abnormal dreams (12% vs 5%). Abnormal dreams occurred in 18% of patients in an unpublished trial (n=950) reported in the package insert for varenicline.

After release, case reports of new onset of psychiatric effects in varenicline users began to arrive at the FDA. On November 20, 2007, the FDA issued an advisory,[7] later updated on February 1, 2008 and on May 16, 2008,[8] regarding a potential for serious neuropsychiatric symptoms. These included behavioral changes, agitation, new onset of depressed mood, suicidal ideation, and reports of completed suicides. The act of smoking cessation and nicotine withdrawal may precipitate new psychiatric symptoms; however, some of the reported events occurred among varenicline users who had not yet stopped smoking. The true incidence of these events among varenicline users is unknown at this time. On the basis of an increasing number of such reports, the FDA has elevated this information to the warning section of the prescribing information and recommended that clinicians monitor all patients for new psychiatric symptoms and that patients report any change in mood or behavior. Data regarding safety in patients with serious preexisting psychiatric conditions are lacking, due to the exclusion of such patients from the original trials.

The cost for varenicline ($126 per month) is comparable to other smoking cessation medications (Table 1) and is considerably less than the cost of two packs of cigarettes per day (approximately $180–230 per month for brand-name cigarettes as of July 2008). Heavy smokers who successfully quit will incur cost savings beginning with the first month of treatment.

Varenicline is an important new drug that is more effective than all existing pharmacotherapies and usually well tolerated except for nausea and abnormal dreams. Cigarette smoking is highly morbid and increases the risk for death from cardiovascular disease, lung disease, and cancer. For many patients, the morbidity of continued smoking is such that a small risk of serious psychiatric adverse events from varenicline may be acceptable to both the patient and clinician. We recommend a full discussion of the risks and potential benefits with each patient who is considering varenicline therapy. This should include an informal, verbal informed consent process. As new data emerge regarding the true incidence of psychiatric side effects, clinicians may need to reassess the proper role of this novel drug.

Aliskiren

Hypertension accounts for more primary care outpatient visits than any other medical condition.[9] Among the 30% of all US adults who are hypertensive, 78% are aware of the condition, and only 68% are treated with medications.[10] Even in the modern era with a multitude of pharmacologic options, only 64% of patients on antihypertensive medication are controlled.[10] In this context, a novel and effective medication to treat patients with hypertension would be welcome.

Table 1. Cost of New Medications Compared to Existing Therapies

New drug	AWP (USD)*	Existing drugs	AWP (USD)	$4 per month option†
Smoking cessation				
Varenicline 1 mg bid	125.84	Nicotine gum 4 mg, 4 per day	47.50	
		Nicotine patch 21 mg qd	76.59	
		Bupropion SR 150 mg bid	120.36	
Hypertension				
Aliskiren 150 mg qd	77.51	Enalapril 10 mg qd	32.16	X
		Lisinopril 10 mg qd	29.70	X
		Losartan 50 mg qd	66.14	
Amlodipine 5 mg/valsartan 160 mg combination pill	77.76	Amlodipine 5 mg plus valsartan 160 mg (two pills)	119.63	
Type 2 diabetes				
Sitagliptin 100 mg qd	189.36	Glyburide 5 mg bid	46.61	X
Exenatide 10 mcg bid	219.00	Metformin 500 mg bid	42.50	X
		Pioglitazone 30 mg qd	206.86	
		NPH insulin, one vial	44.38	
Diabetic neuropathy				
Gabapentin 600 mg tid	208.16	Amitriptyline 25 mg	10.83	X
Pregabalin 150 mg bid	140.52	Carbamazepine 200 mg bid	21.44	X
Duloxetine 60 mg qd	132.50			

**Average wholesale price or generic equivalent average price for 30 days of therapy of intermediate dose of each medication*
†Available for 4 USD per month as loss leader at selected "big box" retail stores as of June 1, 2008
Sources: Price Alert, Wolters Kluwer Health, February 15, 2008. Red Book: Pharmacy's Fundamental Reference. February 2008 Update. Thomson Healthcare. Medical Letter 2007;49:101

Aliskiren is a direct renin inhibitor. Renin inhibitors are the first new class of antihypertensive medications since the release of angiotensin receptor blockers (ARBs) in 1995. Aliskiren, like angiotensin-converting enzyme inhibitors (ACEi) and ARBs, works through the renin-angiotensin-aldosterone system (RAAS), but inhibits this pathway earlier, at the first step. Aliskiren directly inhibits renin activity and thus decreases the conversion of angiotensinogen to angiotensin I. As aliskiren does not increase bradykinin levels, rates of cough and angioedema are less than those of ACEi.

The FDA approved aliskiren in March 2007 based primarily on six studies of 3,961 patients with mild to moderate hypertension. These placebo controlled randomized trials included two published studies of monotherapy,[11,12] two of aliskiren plus valsartan,[13,14] and one of aliskiren plus a thiazide diuretic.[15] These short-term studies evaluated blood pressure reduction as the primary outcome. If one pools the results from the two published studies of monotherapy (n=1,324),[11,12] mean reductions in systolic blood pressure were 5.3, 12.2, 15.3, and 15.8 mmHg for placebo, aliskiren 150 mg, 300 mg, and 600 mg, respectively. This degree of blood pressure reduction is comparable to that seen with existing antihypertensive medications.

The incremental value of adding aliskiren to valsartan monotherapy, while statistically significant, is small and clinically inconsequential. For example, in one trial, mean placebo subtracted systolic and diastolic blood pressure reductions were 8.2/5.6 mmHg for valsartan monotherapy and 12.6/8.1 mmHg for combination therapy.[14]

A more important clinical consideration is the value of adding aliskiren to a thiazide diuretic. Thiazides are synergistic with most antihypertensive medications and should generally be part of any multidrug regimen to treat patients with hypertension. In the trial of Villami and colleagues, aliskiren monotherapy was no more effective than HCTZ monotherapy, an inexpensive drug with an established track record of cardiovascular risk reduction.[15] Combination therapy dosing strategies that included 12.5 or 25 mg of HCTZ, with one exception, were significantly more effective than either drug as monotherapy. For example, placebo subtracted systolic blood pressure reductions for aliskiren 150 mg, HCTZ 12.5 mg, aliskiren 150 mg/HCTZ 12.5 mg, and aliskiren 300 mg/HCTZ 25 mg were 4.8, 6.4, 10.1, and 13.7 mmHg, respectively. As with ACEi and ARBs, aliskiren is less effective in African-American than white hypertensive patients.

The side effect profile for aliskiren is quite favorable. In the pooled labeling information, discontinuation rates due to adverse events were actually less than those for placebo (2.2% vs 3.5%). Cases of angioedema associated with aliskiren have been reported to the FDA; the actual incidence is unknown, but is likely small based on available data and the mechanism of action of the drug. Minor side effects that occur more often than with the placebo include rash (1%), hyperkalemia (0.9%), and diarrhea (2.3%). Cough, the most common reason for discontinuation of ACEi, occurs only rarely with aliskiren (1.1%). Aliskiren, like ACEi and ARBs, is contraindicated during pregnancy.

Aliskiren is considerably more expensive than existing medications that work through the RAAS system (Table 1). Monthly costs are modestly more than for ARBs, but are up to three times more expensive than for ACEi.

Importantly, no published trials have examined the impact of aliskiren on long-term cardiovascular morbidity and mortality. The observation that different classes of antihypertensive agents reduce cardiovascular morbidity to differing degrees, despite comparable blood pressure reduction, has been the single most important conclusion of recent hypertension research. The JNC-7, for example, recommends diuretics as first-line therapy for most patients, based primarily on the preponderance of trials that that have failed to show superiority of any of the new drug classes over thiazides.[16]

It is likely that aliskiren will reduce cardiovascular morbidity to a similar degree as other drugs that work through the RAAS system. However, it is premature to reach this conclusion. At the current time, we know that aliskiren reduces blood pressure to a similar, but not greater, degree than other drug classes. It is well tolerated, but expensive. Less expensive medications exist that have a proven track record in reducing cardiovascular morbidity and for which we have more robust long-term safety data. Pending future research, clinicians should not use aliskiren for initial monotherapy of hypertension. We recommend aliskiren as a potential third line agent for patients with moderate to severe hypertension that is difficult to treat due to side effects or lack of response to multiple other drug classes. It may play a role in resistant hypertension, though this is unstudied to date.

Sitagliptin

Type 2 diabetes is reaching epidemic proportions in developed countries. The rate of rise of the prevalence of type 2 diabetes has paralleled the rise in obesity rates. For example, in the US, the age-adjusted prevalence of diabetes among adults >20 years old has risen from 8.3 to 10.2% from 1988–1994 to 2001–2004.[17] Rates for adults ≥60 years old have increased from 18.9% to 22.5%. Despite awareness of the benefits of tight blood sugar control, the percent of type II diabetics that achieves A1C values <7% has actually dropped from 44.5% to 35% in the past decade.[18]

Sitagliptin is the first in a new class of medications, the dipeptidyl peptidase-4 (DPP-4) inhibitors. To understand this class of medication, one must understand the incretin system. Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are incretins that mediate the effect of a meal on the pancreas. Incretins are gut-derived hormones that are released in a glucose-dependent fashion and bind to and stimulate both beta (GIP and GLP-1) and alpha (GLP-1) cells in the pancreas. This results in increased insulin release and decreased glucagon production, with subsequent lowering of post-meal plasma glucose concentrations. The incretins are degraded promptly by DPP-4 and thus have a short half-life. Sitagliptin inhibits DPP-4, which leads to higher incretin levels and a reduction in post-meal plasma glucose concentration. As incretin release is glucose dependent, sitagliptin does not cause hypoglycemia.

The FDA approved sitagliptin in October 2006 based on studies of monotherapy, combination therapy with pioglitazone, and combination therapy with metformin. Using the study of Aschner and colleagues as an example of the first category of studies, the authors randomly assigned 741 patients with type 2 diabetes to sitagliptin 100 mg or 200 mg monotherapy daily, or to placebo.[19] At 24 weeks, placebo-subtracted reductions in A1C values were 0.79% and 0.94% for 100 mg and 200 mg, respectively. In a study of combination therapy (n=175), the addition of sitagliptin 100 mg daily to

pioglitazone monotherapy lowered A1C values by only 0.70% (CI 0.85–0.54).[20]

Perhaps the most clinically relevant question is the value of adding sitagliptin to metformin monotherapy as the American Diabetes Association now recommends metformin monotherapy at the time of diagnosis for all patients with type 2 diabetes.[21] In a report of 701 patients with type 2 diabetes who had an A1C level between 7–10% despite metformin ≥1,500 mg daily, investigators randomly assigned patients to the addition of sitagliptin 100 mg daily or placebo for 24 weeks.[22] Placebo-subtracted reduction in A1C was 0.69%. In a meta-analysis of seven studies of sitagliptin published after FDA approval, the weighted mean reduction in A1c level for patients treated with sitagliptin was 0.74%.[23]

Sitagliptin lowers A1c to a lesser degree than existing therapies for type 2 diabetes. Mean reductions for different therapies are: insulin intensive (1.5–2.4%), insulin conventional (0.2–0.9%), sulfonylureas (1.1–1.9%), metformin (0.9–1.4%), glitazones (0.9–1.5%), exenatide (0.4–0.9%), and sitagliptin (0.6–0.8%).[24]

Sitagliptin is generally well tolerated. It is weight neutral, and in the pooled results from the prescribing information, only upper respiratory infections (6.3% vs 3.4%) and headache (5.1% vs 3.9%) were more common with sitagliptin compared to placebo. However, the long-term safety is unknown. DPP-4 exists not only in the pancreas, but also is ubiquitous throughout the body.[25] Therefore, there is a potential for unintended consequences of DPP-4 inhibition that will necessitate careful post-marketing surveillance. In addition, the available data are for A1c values as a surrogate endpoint. No data exist regarding the impact of sitagliptin on clinical outcomes in diabetic patients. Sitagliptin is expensive (Table 1) and costs more than four times as much as glyburide, another potential second-line oral agent for type 2 diabetes.

To summarize the existing data, sitagliptin is less effective and more expensive than other agents for type 2 diabetes. The long-term safety is unknown. For these reasons, we do not recommend sitagliptin as either initial or second-line therapy for patients with type 2 diabetes. It may have a limited role in the patient who is unwilling to give injections and whose A1C is above goal despite a regimen of two or three other oral agents.

PHARMACOLOGIC MANAGEMENT OF COMMON CONDITIONS

Diabetic Neuropathy

Diabetic neuropathy is a common complication of diabetes that substantially affects quality of life. However, no guidelines for treatment of diabetic neuropathy are available. To guide clinicians, Wong and colleagues conducted a systematic review of randomized controlled trials that compared oral and topical medications to placebo for adults with painful diabetic neuropathy.[26]

The authors identified 25 eligible studies that evaluated anticonvulsants (n=1,270), antidepressants (n=94), opioids (n=329), and capsaicin (n=277). The primary outcome was dichotomous information for 50% or moderate reduction of pain. Secondary outcomes were 30% reduction of pain and withdrawal due to adverse events. The authors calculated meta-analytic estimates for odds ratios (OR) for each outcome, but did not provide information on the absolute magnitudes of treatment benefits and withdrawal rates.

Table 2 summarizes the pooled odds ratios for efficacy (50% or moderate pain relief) and withdrawal due to adverse events for the different drugs. Among antidepressants, tricyclics demonstrated the greatest efficacy and the lowest likelihood of withdrawal. In contrast, citalopram had low efficacy and a higher likelihood of withdrawal. High-dose duloxetine appeared to be less efficacious and was more likely to lead to withdrawal due to adverse events than low-dose duloxetine.

Among the anticonvulsants, the traditional agents, carbamazepine and sodium valproate, were significantly more likely to be efficacious than to require withdrawal due to adverse events. In contrast, the newer agents, gabapentin and pregabalin, had similar odds ratios for efficacy and withdrawal.

Three studies of opioids met the authors' inclusion criteria. Two studies evaluated controlled release oxycodone with a daily dose range from 10–120 mg. One study evaluated tramadol at daily doses from 200–400 mg; for the purposes of the meta-analysis, the authors considered this an opioid. The opioids were third in effectiveness, after tricyclics and traditional anticonvulsants. Withdrawal rates for opioids were high. Capsaicin cream was relatively less effective and had a high odds ratio for withdrawal.

The authors concluded that tricyclic antidepressants, traditional anticonvulsants, and opioids were more effective than newer generation antidepressants and anticonvulsants. As the treatment period was less than 6 months in all studies, long-term safety and efficacy of these medications strategies are unknown. Based on this systematic review, the authors proposed a treatment algorithm that recommends in sequence: capsaicin or a tricyclic antidepressant, traditional anticonvulsants, newer generation anticonvulsants, duloxetine, and finally opioids. We concur with this approach.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of mortality in the US and a major source of

Table 2. Medications Used in the Treatment of Diabetic Neuropathy

Medication class	No. of studies	Pooled odds ratio (95% CI)	
		Efficacy*	Withdrawal
Antidepressants			
•Tricyclic antidepressants	3	22.24 (5.83–84.75)	2.32 (0.56–9.69)
•Citalopram	1	3.5 (0.3–38.2)	5.6 (0.3–38.2)
•Duloxetine 60 mg	2	2.55 (1.73–3.77)	2.36 (1.05–5.35)
•Duloxetine 120 mg	2	2.10 (1.03–4.27)	4.65 (2.18–9.94)
Anticonvulsants			
•Traditional†	3	5.33 (1.77–16.02)	1.51 (0.33–6.96)
•Newer generation‡	4	3.25 (2.27–4.66)	2.98 (1.75–5.07)
Opioids	3	4.25 (2.33–7.77)	4.06 (1.16–14.21)
Topical agents			
•Capsaicin	1	2.37 (1.32–4.26)	4.02 (1.45–11.16)

*Odds ratio for 50% or moderate reduction in pain compared to placebo
†Carbamazepine, sodium valproate
‡Gabapentin, pregabalin
Data from Wong MC, Chung JWY, Wong TKS. BMJ 2007;335:87

morbidity and mortality worldwide.[27] Two recent guidelines present updated evidence on the management of COPD. In 1998, the US National Heart, Lung, and Blood Institute and the World Health Organization formed the Global Initiative for Chronic Obstructive Lung Disease (GOLD). The GOLD group published their initial consensus report, Global Strategy for the Diagnosis, Management, and Prevention of COPD, in 2001[28] and an updated report in May 2007.[29] The second guideline is from the American College of Physicians (ACP) in November 2007.[30] Concordant recommendations of these two groups and supplemental findings from the recent literature follow.

Both guidelines use the GOLD spirometric classification that stratifies patients into four stages: mild, moderate, severe, and very severe (Table 3). Treatment can decrease symptoms and/or complications, but does not modify long-term decline in lung function. In contrast, smoking cessation is the most effective and cost-effective intervention to reduce the risk of developing COPD and to slow its progression.

Patients should use short-acting bronchodilators on an as-needed basis rather than on a schedule. The combination of albuterol plus ipratropium improves airflow obstruction (as measured by FEV1) and reduces exacerbation rates to a greater degree than either drug alone.

The GOLD authors defined four evidence categories ranging from A (randomized controlled trials with a rich body of data) to D (panel consensus judgment). Clinicians should prescribe one of the following maintenance monotherapies for patients with moderate to severe symptomatic COPD: long-acting inhaled β-agonists, long-acting inhaled anticholinergics, or inhaled corticosteroids (evidence level A). The long-acting β-agonists and anticholinergics are more effective and convenient than short-acting bronchodilators. They improve health status and reduce the rate of COPD exacerbations. The ACP recommends inhaled corticosteroids as an option for daily long-acting monotherapy in patients with moderate COPD. In contrast, the GOLD group recommends reserving them for patients with severe COPD who experience frequent exacerbations as an addition to other long-acting treatments. Which long-acting agent is the best choice? Salmeterol, tiotropium, and inhaled corticosteroids are similarly effective in reducing the frequency of COPD exacerbations (Table 4).[31]

Several recent studies have evaluated the benefit of combination long-acting inhalers. In a study of patients with moderate COPD, tiotropium alone and tiotropium + salmeterol were comparable in preventing exacerbations, improving quality of life, and decreasing hospitalizations.[32] Tiotropium + salmeterol/fluticasone prevented exacerbations comparably to tiotropium alone, but improved quality of life and decreased hospitalization rates. In the TORCH trial, the authors similarly evaluated long-acting combination therapy in patients with moderate COPD.[33] The primary outcome was death. The combination of salmeterol and fluticasone decreased exacerbations, improved health status, and improved spirometry compared to either agent as monotherapy. There was a nonsignificant trend towards a decrease in death rates for combination therapy [HR 0.825 (95% CI 0.68–1.02) p=0.052].

Finally, consider pulmonary rehabilitation earlier in the course of the disease. Patients with moderate to very severe COPD experience improved exercise tolerance and decreased dyspnea and fatigue (evidence level A).[34] Patients benefit most from a comprehensive program that addresses exercise deconditioning, social isolation, depression, muscle wasting, and weight loss. Patients who continue exercise training at home are most likely to maintain improved health status after completion of formal rehabilitation (evidence level B).[35]

In summary, available data support the use of long-acting monotherapy for symptomatic patients with moderate COPD: long-acting β-agonist, long-acting anticholinergic, or inhaled corticosteroids. Long-acting combination therapy is an appropriate next step for the patient who remains symptomatic. Salmeterol-fluticasone or salmeterol-fluticasone + tiotropium are superior to tiotropium + salmeterol. Unanswered questions regarding inhaled steroids are: (1) Is there a dose-response relationship? (2) What is their long-term safety?

Table 3. GOLD Criteria for the Spirometric Classification of COPD Severity

Stage	Severity	FEV1/FVC	FEV1 (% predicted)
1	Mild	<0.70	≥80%
2	Moderate	<0.70	50%≤FEV1<80%
3	Severe	<0.70	30%≤FEV1<50%
4	Very severe	<0.70	<30% or <50% and pO2<60

Adapted from Rabe KF, Hurd S, Anzueto A, et al. Am J Respir Crit Care Med 2007;176:532

Table 4. Effectiveness of Inhaled Medications in Reducing COPD Exacerbation Rates

Inhaled medication	No. of studies	Pooled relative risk of exacerbation (95% CI)
Long-acting beta agonists	9	0.79 (0.69–0.90)
Tiotropium	5	0.77 (0.71–0.84)
Inhaled corticosteroids	6	0.76 (0.72–0.80)

Data from Sin DD, McAlister FA, Paul Man SF, Anthonisen NR. JAMA 2003;290:2301

Resistant Hypertension

Resistant hypertension, defined as blood pressure >140/90 despite maximum doses of three drugs, including a diuretic, is a common clinical problem. The cause of resistant hypertension is often multifactorial. Common factors include obesity, excess alcohol intake, excess salt intake, nonadherence to treatment, and a secondary cause, such as primary aldosteronism or renal artery stenosis. The incidence of the various causes depends on the population studied.

Emerging evidence suggests that adherence rates are higher for fixed-dose combination pills than for separate hypertensive agents. For example, Gerbino and Shoheiber conducted a 1-year study of patients who received at least two prescriptions for a fixed-dose amlodipine-benazepril (one pill) or for both a dihydropyridine calcium channel blocker and an ACE inhibitor (two pills).[36] Adherence rates were higher with the fixed-dose (one pill) treatment than with treatment with two pills (88% vs 69%, p<0.0001). In addition, combination pills may actually be less expensive than single agents (two pills) (Table 1).

As volume overload is common, an important strategy is to add or increase diuretics. Up to 60% of hypertensive patients may respond to this approach. The usual dose for hydrochlorothiazide (HCTZ) is 12.5–25 mg daily in a patient with normal renal function. Increasing the dose from 25 to 50 mg daily may further decrease blood pressure, but at the expense of higher rates of hypokalemia. Chlorthalidone 25 mg has a longer half-life than HCTZ (30 h vs 8 h) and is more effective in lowering nighttime blood pressure. The American Heart Association recommends chlorthalidone as its thiazide of choice for patients with resistant hypertension.[37] A loop diuretic is preferable to a thiazide if the glomerular filtration rate (GFR) is less than 30 ml/min or if the creatinine is >2 mg/dl. Patients should take short-acting loop diuretics, including furosemide, twice a day: e.g., furosemide 20–80 mg bid. Once daily use of a short-acting loop diuretic leads to reactive sodium retention and inadequate blood pressure control. Patients can take a long-acting loop diuretic, such as torsemide, once a day.

Good evidence supports adding spironolactone as a strategy to treat resistant hypertension. The ASCOT-BPLA trial analyzed the effect of spironolactone (mean dose 25 mg daily) as fourth-line treatment in patients who were not controlled on three drugs.[38] Blood pressure fell by an average of 22/10 mgHg. Adverse effects included gynecomastia (6%) and hyperkalemia (2%). Patients with and without primary aldosteronism responded to spironolactone. In patients without primary aldosteronism, doses of spironolactone <50 mg lowered blood pressure. Patients with primary aldosteronism required substantially higher doses (up to 400 mg).[39] Current recommendations are to screen for primary aldosteronism in patients with an adrenal incidentaloma or unprovoked hypokalemia[40] and if blood pressure remains poorly controlled after adding spironolactone 100 mg daily.[39,40] It is important to recheck serum creatinine and electrolytes after 1 week on spironolactone and after each dose titration. Avoid spironolactone in patients with moderate chronic kidney disease.

Nighttime dosing of one drug in a multi-drug regimen is another potential strategy. In a recent trial of patients with resistant hypertension (n=250), investigators randomly assigned patients to receive one of their drugs at bedtime versus usual care.[41] Bedtime treatment resulted in a 9-mmHg drop in mean systolic blood pressure.

Implications for practice are to: (1) consider using fixed combination drugs to improve adherence and potentially decrease cost, (2) include a diuretic in multi-drug regimens and diurese patients aggressively, (3) add spironolactone if needed, and (4) consider giving one drug at bedtime to improve morning blood pressure control.

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