

Pharmacotherapy Perspectives

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New Drugs

What's important and what's not: Part 1

Introduction

The deluge of new drugs has continued into the new millennium. The U.S. Food and Drug Administration (FDA) approved 35 new molecular entities (NMEs) and six new biologicals in 1999, following on the heels of 30 NMEs and seven biologicals in 1998.^{1,2} Table 1 lists the 1999 drug approvals by treatment area. The table includes the NMEs and some notable dosage form changes in oral pain medications.

In addition to new drugs, there are new guidelines, a new emphasis on follow-up care to make sure patients attain blood sugar, cholesterol and blood pressure goals, and new discussions about the place of new drugs and cost benefits in patient care. Intense multimedia advertising to consumers influences prescribing choices and has even changed medical terminology. For example, impotence has become "erectile dysfunction" and incontinence has been transformed into "overactive bladder." New developments in patent law have made biological entities like enzymes patentable, resulting in new opportunities for academic institutions and biotech companies to earn unprecedented fortunes.

One of the most interesting questions is where new drugs fit in our current therapeutic emporium and how marketing techniques may succeed when therapeutic merit alone fails to persuade providers.

How quickly are new drugs integrated into clinical practice?

A closer look at table 1 on the next page or its 1998 counterpart does not reveal many familiar generic or trade names. Although it does take time for newer drugs to gain market penetration, the number of these recent drugs in everyday use is small. Recently approved drugs that have appeared in the top 200 brand-name prescription drugs of 1999 are listed in Table 2.³

Popularity vs importance

The importance of newer medications cannot be judged only by their acceptance into ambulatory therapy. The relative popularity of medications on the list reflects physician preference, influenced increasingly by patient requests resulting from direct-to-consumer drug advertising. Good examples of medications that may have benefited from heavy television advertising are numbers 30 and 31 on the Top 200 list, Allegra® (fexofenadine) and Zyrtec® (cetirizine). Both are active metabolites of well-known parent drugs and both are advertised to consumers as therapeutic advances in allergy treatment. The advertisements are slightly misleading. In fact, Allegra® was developed to replace a more toxic parent,

Seldane® (terfenadine), and the most notable achievement of both metabolites is to provide the manufacturers with virtual patent extensions of the parent drugs.⁴ Initial efficacy studies of fexofenadine were available only as summaries in the package insert when the product was first marketed. The recent introduction of a 180-mg dosage form of Allegra® for allergic rhinitis renews questions about the efficacy of the 60-mg dose.⁵ Even worse, the higher dose now has been associated with QT prolongation and polymorphic ventricular tachycardia, the problem that caused withdrawal of Seldane® from the market.⁶

Table 2. Recently Approved Drugs in the Top 200 Prescription Drugs

Rank	Trade Name	Generic Name	Approval Year
18	Celebrex®	celecoxib	1998
37	Viagra®	sildenafil	1998
69	Celexa®	citalopram	1998
72	Nasonex®	mometasone furoate	1997
75	Singulair®	montelukast	1998
80	Rezulin®	troglitazone	1997
82	Vioxx®	rofecoxib	1999
97	Plavix®	clopidogrel	1997
103	Evista®	raloxifene	1997
107	Detrol®	tolterodine	1998
109	Avapro®	irbesartan	1997
136	Flomax®	tamsulosin	1997
178	Baycol®	cerivastatin	1997

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The information given and views expressed herein do not necessarily reflect the opinions of PSW, its Board or members.

Table 1. 1999 Drug Approvals

Treatment Area	Drug	Trade name	Manufacturer	Indication/ Action
AIDS	alitretinoin gel*	Panretin	Ligand	Kaposi's Sarcoma
	amprenavir	Agenerase	Glaxo-Wellcome	HIV infection
Anesthesia	dexmedetomidine	Precedex	Abbott	Tracheal intubation
	rapacuronium	Raplon	Organon	Tracheal intubation
Anti-infective	dalfopristin-quinupristin	Synercid	Aventis	Vancomycin-resistant infections
	gatifloxacin	Tequin	BM Squibb	Quinolone po, injectable
	moxifloxacin	Avelox	Bayer	Quinolone
	oseltamivir	Tamiflu	Roche	Influenza A and B
	zanamavir for inhalation	Relenza	Glaxo Wellcome	Influenza A and B
Arthritis	rofecoxib	Vioxx	Merck	Osteoarthritis, pain, dysmenorrhea
Cancer	bexarotene* (po)	Targretin	Ligand	Cutaneous T-cell lymphoma
	cytarabine liposome, intrathecal	DepoCyt	Depotech	Intrathecal lymphomatous meningitis
	denileukin diftitox (IV)	Ontak	Ligand	Recurrent T-cell lymphoma
	epirubicin (IV)*	Ellence	Pharmacia/ Upjohn	Early breast cancer
	exemestane (po)*	Aromasin	Pharmacia/ Upjohn	Advanced breast cancer
	temozolomide* (po)	Temodar	Schering	Refractory anaplastic astrocytoma
Cardiovascular	cilostazol	Pletal	Otsuka	Intermittent claudication
	dofetilide (po)	Tikosyn	Pfizer	Atrial fib/flutter Class III antiarrhythmic
	eprosartan	Teveten	Unimed	Hypertension
Dermatology	aminolevulinic acid, topical	Levulan	DUSA/Berlex	Actinic keratoses
	mequinol/tretinoin, topical	Solage	BM Squibb	Solar lentigines
Endocrine	conjugated estrogens, plant-derived	Cenestin	Duramed	Vasomotor symptoms of menopause
	doxercalciferol	Hectorol	Bone Care Int	Elevated parathyroid hormone
	ganirelix acetate (SC)	Antagon	Organon	Infertility (GnRH antagonist)
	orlistat	Xenical	Hoffman-LaRoche	Obesity
	pioglitazone	Actos	Takeda	Type 2 diabetes
	rosiglitazone	Avandia	SKB	Type 2 diabetes
Eye	ketotifen fumarate 0.025%	Zaditor	CibaVision	Allergic conjunctivitis
	pemirolast potassium 0.1%	Alamast	Santen	Allergic conjunctivitis
G-I	rabeprazole	AcipHex	Esai/Janssen	GERD, DU, Z-E
Hematology	sodium ferric gluconate injectable	Ferrlecit	R&D Labs	Iron deficiency anemia
Neurology	entacapone	Comtan	Novartis/Orion	Parkinson's Disease (COMT inhibitor)
	levetiracetam	Keppra	UCB Pharma	Partial onset seizures
	zaleplon	Sonata (C-IV)	Wyeth-Ayerst	Insomnia
Pain	hydrocodone 5, 7.5 and 10 mg with acetaminophen 400 mg	Zydone# (C-III)	Endo	Pain
	lidocaine 5% patch	Lidoderm	Endo	Post-herpetic neuralgia
	oxycodone/acetaminophen 2.5/325, 5/325, 7.5/500, 10/650	Percocet 2.5, 5, 7.5 and 10 mg (C-II)	Endo	Pain
Pulmonary	levalbuterol.HCl	Xopenex	Sepracor	Bronchospasm
	nitric oxide*	INOMax	INO Therapeutics	Hypoxic respiratory failure in neonates
	poractant*	Curosurf	Dey	Infant resp. distress syndrome
Radiology	gadoversetamide	Optimark	Mallinckrodt	MRI contrast agent
Transplant	sirolimus	Rapamune	Wyeth-Ayerst	Renal transplant

* denotes orphan drug # not to be confused with Zyban, Zydys, Zylfo, Zylprim, Zymacap, Zymase, Zyprexa, or Zyrtec

New medications for major indications

A more productive approach may be to look at what kinds of problems are being addressed by the most frequently prescribed drugs. Are the important public health problems of the millennium like heart disease, cancer, diabetes, asthma and mental illness being treated? Table 3 lists the numbers of Top 50 brand name and generic prescription drugs of 1999 by therapeutic categories.^{3,7}

Categories with the largest number of drugs were blood pressure, infectious disease, mental health and pain. The mental health drugs included antidepressants, anti-anxiety agents and drugs for attention deficit disorder with hyperactivity; no antipsychotics were in the top 50. Viagra® was arbitrarily assigned to the replacement category, along with Synthroid® and Levoxyl®. Categories with no representation included cancer, because so few of the drugs used in chemotherapy are used as oral dosage forms.

A broader view of what's new in the treatment of two of these conditions illustrates that it is not only the drugs themselves, but also the approaches to using medication, which can promote advances in patient care and patient health. Two examples follow. One is hypertension, an area where there have been only modest recent advances, and diabetes, where care for Type 2 diabetes has been transformed by a number of new oral medications.

Hypertension

There is no longer any question that reduction of high blood pressure reduces the risk of stroke, coronary heart disease, renal failure and death from all causes. Yet, no more than 50% of patients treated for hypertension achieve adequate control, judged by guideline recommendations.^{8,9} Many patients still discontinue their drug therapy within the first six months. Part of the problem is that most hypertensive patients will not reach their blood pressure goals with monotherapy.⁸ Many physicians hesitate to add a second drug. As long as brand-name antihypertensives are advertised as being superior to competitors, the false hope of successful monotherapy will be prolonged. On the other hand, dose titration and stepped therapy with drug combinations can help the great majority of patients to reach their goals. Unless that expectation is stated expressly when the patient's treatment plan is initiated, both physician and patient may be faced with a sense of failure if one medication is not enough. Table 4 reproduces the JNC VI guidelines for hypertension treatment with blood pressure goals stratified according to risk factors.

Drug combinations may work well because smaller doses of each component may be effective and at the same time decrease the incidence of noticeable adverse effects.

The initial guideline drug choices for uncomplicated hypertension are still diuretics and beta-blockers.⁹ Choices in the

Table 3. Treatment Categories of the Top 50 Brand-Name and Generic Prescription Drugs of 1999

Treatment Category	Generic Drugs	Brand-Name Drugs	Total Number
Allergy	1	5	6
Arthritis	1	1	2
Asthma	2	0	2
Blood Pressure	8	11	19
CNS-other	2	3	5
Cardiovascular	3	4	7
Cough-cold	2	0	2
Contraception	0	1	1
Diabetes	2	3	5
G-I	2	2	4
Infection	7	7	14
Lipids	1	3	4
Mental health	7	5	12
Osteoporosis	2	3	5
Other	3	0	3
Pain	7	1	8
Replacement	0	3	3

Brand-Name Top 50 do not appear to reflect the guideline advice. Out of the eleven antihypertensives in the Brand-Name Top 50, only one, Toprol XL®, #38, is a beta-blocker. There are three calcium channel blockers, five ACE inhibitors, one alpha-blocker and one angiotensin-receptor antagonist. In contrast, atenolol is #2 on the Generic Top 50, with over 31 million prescriptions dispensed. There have been no new first-line agents for some time. Recent new drugs have included three angiotensin-receptor antagonists (Micardis®, Atacand® and Teveten®), and less recently, ACE inhibitor-calcium channel blocker combinations like Lotrel® (benazepril plus amlodipine).

What is new in hypertension treatment is not any one antihypertensive drug, but new attitudes toward using all the available drugs more effectively. What is new in JNCI VI is the concept of risk stratification, so those patients at higher risk have lower goal blood pressures and begin drug therapy at once in addition to lifestyle modification.^{9,10} What is new is the improvement in government websites like the National Heart, Lung, and Blood Institute (NHLBI) site which is the source of Table 4. Web visitors are encouraged to download the entire JNC VI report or the two-page summary reproduced here. The information summary is also available as a laminated card that can be ordered at no charge on the website.⁹ For many busy practitioners, this means that information formerly available to those with access to the Archives of Internal Medicine can

now be viewed and reviewed as a wall-chart in any practitioner's office. Patients who read this information are now reading from the same page as their caregivers and have more incentive for becoming their own care managers.

What also is new in JNC VI is the recommendation that outcomes of antihypertensive therapy be evaluated not only in the short term, but also in intermediate- and long-term time frames.¹¹ In the short term, blood pressure control is important, but does control in the long run decrease heart attacks and save lives?

Table 4. The JNC VI Guide to Prevention and Treatment of Hypertension Recommendations

Blood Pressure Measurement	<p><u>Patient should:</u></p> <ul style="list-style-type: none"> - Rest for 5 minutes before measurement. - Refrain from smoking or ingesting caffeine for 30 minutes prior to measurement. - Be seated with feet flat on floor, back and arm supported, arm at heart level. <p><u>Clinician should:</u></p> <ul style="list-style-type: none"> - Use the appropriate size cuff for the patient; the bladder should encircle at least 80 percent of the upper arm. - Use calibrated or mercury manometer. - Average two or more readings, separated by at least 2 minutes.
Primary Prevention	<p>Encourage patients to make healthy lifestyle choices:</p> <ul style="list-style-type: none"> - Quit smoking to reduce cardiovascular risk. - Lose weight, if needed. - Restrict sodium intake to no more than 100 mmol per day. - Limit alcohol intake to no more than 1-2 drinks per day. - Get at least 30-45 minutes of aerobic activity on most days. - Maintain adequate potassium intake—about 90 mmol per day. - Maintain adequate intakes of calcium and magnesium.
Goal	<p>Set a clear goal of therapy based on patient's risk. Control blood pressure to below:</p> <ul style="list-style-type: none"> - 140/90 mm Hg for patients with uncomplicated hypertension; set a lower goal for those with target organ damage or clinical cardiovascular disease. - 130/85 mm Hg for patients with diabetes. - 125/75 mm Hg for patients with renal insufficiency with proteinuria greater than 1 gram per 24 hours.
Treatment	<p>Begin with lifestyle modifications (see primary prevention box) for all patients. Be supportive!</p> <ul style="list-style-type: none"> - Add pharmacologic therapy if blood pressure remains uncontrolled. - Start with a diuretic or beta-blocker unless there are compelling indications to use other agents. Use low dose and titrate upward. Consider low dose combinations. - If no response, try a drug from another class or add a second agent from a different class (diuretic if not already used).
Adherence	<ul style="list-style-type: none"> - Encourage lifestyle modifications. Be supportive! - Educate patient and family about disease. Involve them in measurement and treatment. - Maintain communications with patient. - Discuss how to integrate treatment into daily activities. - Keep care inexpensive and simple. - Favor once-daily, long-acting formulations. - Use combination tablets, when needed. - Consider using generic formulas or larger tablets that can be divided. This may be less expensive. - Be willing to stop unsuccessful therapy and try a different approach. - Consider using nurse case management.

JNC VI Risk Stratification and Treatment Recommendations

- Determine blood pressure stage.
- Determine risk group by major risk factors and TOD/CCD.
- Determine treatment recommendations (by using the table below).
- Determine goal blood pressure.
- Refer to specific treatment recommendations.

Major Risk Factors

- Smoking
- Dyslipidemia
- Diabetes mellitus
- Age > 60 years
- Gender :
 - Men
 - Postmenopausal women
- Family history :
 - Women < age 65
 - Men < age 55

TOD/CCD (Target Organ Damage/ Clinical Cardiovascular Disease)

- Heart diseases
- LVH
 - Angina/prior MI
 - Prior CABG
 - Heart failure
- Stroke or TIA
Nephropathy
Peripheral arterial disease
Hypertensive retinopathy

Blood pressure stages (mm Hg)	Risk Group A No major risk factors No TOD/CCD	Risk Group B At least one major risk factor, not including diabetes No TOD/CCD	Risk Group C TOD/CCD and/or diabetes, with or without other risk factors
High-normal (130-139/85-89)	Lifestyle modification	Lifestyle modification	Drug therapy for those with heart failure, renal insufficiency or diabetes. Lifestyle modification
Stage 1 (140-159/90-99)	Lifestyle modification (up to 12 months)	Lifestyle modification (up to 6 months). For patients with multiple risk factors, clinicians should consider drugs as initial therapy plus lifestyle modifications.	Drug therapy Lifestyle modification
Stages 2 and 3 (≥160/≥100)	Drug therapy Lifestyle modification	Drug therapy Lifestyle modification	Drug therapy Lifestyle modification

Example: A patient with diabetes and a blood pressure of 142/94 mm Hg plus left ventricular hypertrophy should be classified as having stage 1 hypertension with target organ disease (left ventricular hypertrophy) and with another major risk factor (diabetes). This patient would be categorized as **Stage 1, Risk Group C**, and recommended for immediate initiation of pharmacologic treatment.

Goal Blood Pressure

<140/90 mm Hg	Uncomplicated hypertension, Risk Group A, Risk Group B, Risk Group C except for the following:
<130/85 mm Hg	Diabetes; renal failure; heart failure
<125/75 mm Hg	Renal failure with proteinuria > 1 gram/24 hours

SPECIFIC TREATMENT RECOMMENDATIONS

Lifestyle modification should be definitive therapy for some patients and adjunctive therapy for all patients recommended for pharmacologic therapy. Turn page over for a list of recommended lifestyle modifications.

INITIAL DRUG CHOICES

- Start with a low dose of a long-acting once-daily drug, and **titrate dose**
- Low-dose combinations may be appropriate

Uncomplicated Hypertension

Diuretics
Beta-blockers

Compelling Indications

Diabetes type 1 (IDDM)	start with ACE inhibitor if proteinuria is present
Heart failure	start with ACE inhibitor or diuretic
Myocardial infarction	beta-blocker (non-ISA) after MI; ACE inhibitor for LV dysfunction after MI
Isolated systolic hypertension (older patients)	diuretics (preferred) or calcium antagonists (long-acting DHP)

Specific Indications for the Following Drugs:

(See Table 9 in JNC VI for specific indications)

ACE inhibitors
Angiotensin II receptor blockers
Alpha-blockers
Alpha-beta-blockers
Beta-blockers
Calcium antagonists
Diuretics

Diabetes

The idea of care as a partnership between the patient, his family and the entire team of health care providers is more familiar to patients with diabetes.¹² In the last few years, diabetes care has also been improved by three new classes of oral drugs. Unfortunately, one of the new drugs, Rezulin® (troglitazone) was withdrawn from the market on March 21, 2000.¹³ The FDA asked the manufacturer to withdraw the drug because of liver toxicity that occurred at a higher frequency than in the two thiazolidinediones that were released last year, Actos® (pioglitazone) and Avandia® (rosiglitazone). The symptoms of hepatotoxicity in affected patients included nausea, fever, pruritus, malaise and jaundice, with findings of subacute hepatic necrosis, fibrosis and cholestasis.¹⁴ Although toxicity is usually reversible on discontinuation of the drug, 63 deaths were linked to the drug.¹⁵ One report in the online media quoted a patient on Rezulin® who became ill, and whose liver enzyme elevations became evident only because she insisted that her physician perform liver function tests. Her comment was, "A lot of doctors (including hers) were involved in the initial studies on Rezulin® and I think that skews their perception of the drug."¹⁵ The drug represented an important therapeutic advance and was well tolerated by a majority of patients. Only 2.2% of 2510 North American patients in pre-marketing trials had elevations in alanine aminotransferase, and only two patients had reversible jaundice.¹⁴ Liver failure was a very rare idiosyncratic reaction that became evident only when millions of patients worldwide were taking the drug.

The question now is whether the two alternative medications are really safer. The FDA, according to Dr. Janet Woodcock, Director of the FDA Center for Drug Evaluation and Research, after reviewing pre- and post-marketing safety data for all three drugs, has concluded that Actos® and Avandia® are indeed safer.¹³ Although only 0.2% of patients in pre-marketing trials of rosiglitazone had ALT levels greater than three times normal (identical to placebo patients), one case of reversible hepatotoxicity has been reported with post-marketing rosiglitazone use.¹⁶ The onset of symptoms (nausea, vomiting, abdominal pain, fatigue, chills, dark urine and elevations of ALT and AST) occurred two weeks after the patient started taking the drug. It is not clear that rosiglitazone alone was responsible for the problem because the patient also had a history of one week of troglitazone therapy eight months prior to this occurrence. The authors of this case study recommended that liver enzymes be checked more frequently early in therapy, weekly for two to four weeks, then monthly for the remainder of the first year. Early detection of the problem is the key to safety.

Important Therapeutic Advances

Without the convenience of hindsight, it is difficult to designate the best candidates for meaningful advances in drug

therapy. Orphan drugs were not included for consideration because their application is relatively narrow. The following examples are good examples of achievements in pharmaceutical research that will have broad applications to better patient care. Some may have far-reaching consequences in the future, like the possibility of chemoprevention of colorectal cancer on a large scale, or the elimination of the major toxicities associated with bone marrow transplantation.

1. Synercid® (quinupristin-dalfopristin)

Antibiotic resistance begins with the exposure of bacteria to antibiotics. In the case of vancomycin-resistant enterococci (VRE), these bacteria, once introduced, persist indefinitely not only in fecal material of patients, but also in the health care environment on any available surface, including IV poles, floors and mattresses.¹⁷ The bacteria then can be spread from patient to patient by unwashed hands of health care workers. Small violations of conventional infection control procedures can initiate a catastrophe. Hospitals have successfully reduced antimicrobial resistance by restricting antibiotic use and doing surveillance cultures of high-risk patients followed by patient isolation where appropriate. Pre-emptive techniques have included practitioner education on appropriate prescribing and patient education that antibiotics may not be useful in many common infections.¹⁸ Unnecessary and empiric prescribing could be greatly reduced if improved rapid diagnostic tests, available perhaps at the bedside, could provide instant access to bacterial culture and sensitivities. The other great hope is that new antibiotics will continue to be developed at a rate that at least matches the rate at which older antibiotics become ineffective against bacteria that have developed resistance. Streptogramins, a new class of antibiotics, are effective against VRE.

Synercid®, a 30:70 combination of two streptogramin antibiotics, quinupristin and dalfopristin, is a drug of last resort that is now available to treat life-threatening infections caused by vancomycin-resistant *Enterococcus faecium*, and also antibiotic-resistant staphylococcal and streptococcal infections. Prior to Synercid®, there was no effective drug to treat vancomycin-resistant infections. One survey in 1997 reported that between 1988 and 1996, there was a nearly 50-fold increase in rates of vancomycin-resistant *Enterococcus* infections in the United States.¹⁹ At that point, 6-8% of the *E faecium* samples were resistant to Synercid®. Because measurable resistance was evident two years before the drug was even marketed, Synercid® should be used extremely selectively if it is to remain effective. In 1997, the incidence of methicillin-resistance was 30% in *Staphylococcus aureus* and 70% in other species of *Staphylococcus*. In 1997-98, the overall rate of *Streptococcus pneumoniae* strains with penicillin resistance was 29.5%.²⁰ Synercid® is clearly a temporary answer to a growing problem.

2. COX-2 Inhibitors: Celebrex® (celecoxib) and Vioxx® (rofecoxib)

The discovery that cyclooxygenase, the key enzyme in the transformation of arachidonic acid to prostaglandins, existed in two isoforms with separate physiologic functions, has made possible the development of safer non-steroidal anti-inflammatory drugs (NSAIDs).²¹ The new inducible isoform, named COX-2, was identified in 1990, and the pharmaceutical industry has already developed and marketed two drugs designed to inhibit COX-2 selectively. The constitutive form of the enzyme, COX-1, constantly present in tissues, catalyzes the synthesis of prostaglandins with important physiologic functions like protection of gastric mucosa, maintenance of renal blood flow and conservation of platelet integrity. In contrast, COX-2 normally is not present in most tissues, but is induced by mediators of inflammation that respond to inflammatory stimuli. Traditional NSAIDs inhibited the production of both helpful and harmful prostaglandins, so that relief of inflammation and pain was achieved only at the price of possible gastric and renal toxicity.

The COX-2 inhibitors are designer drugs, artfully developed to exploit structural differences between COX-1 and COX-2. X-ray crystallography of the 3-D structure of COX-2 showed structural differences between COX-1 and COX-2.²¹ Both isoforms had a hairpin-shaped structure, but COX-2 had a more flexible roof, a side-pocket with a possible drug-binding site and a wider entry channel. Progressive modification and addition of bulky side chains to non-selective NSAIDs like flurbiprofen produced prototypes of selective COX-2 inhibitors that did bind in the COX-2 side-pocket, but were too large to fit in the COX-1 channel. In less than ten years, exciting basic research progressed through preclinical and clinical trials to result in the marketing of two COX-2 inhibitors. Celecoxib was initially marketed to treat osteoarthritis and rheumatoid arthritis, while the indications for rofecoxib are osteoarthritis and acute pain, including dysmenorrhea.²² For long-term use, the promise of greater safety in COX-2 selective agents may reduce gastrointestinal and other toxicities for patients at greater risk.

One of the most exciting new strategies for fighting cancer is the field of chemoprevention. This year, celecoxib has also been approved for the adjunctive treatment of familial adenomatous polyposis (FAP).²³ FAP is a rare hereditary disorder that almost always results in the development of colon cancer by age 40-50 in affected family members. A small study in 83 FAP patients taking celecoxib 400 mg po BID showed that after six months, the mean reduction in the number of colorectal polyps was 28%, compared to 5% for placebo ($p < 0.003$).²⁴ This short-term study was not long enough to show any effect on the development of cancer.

Celecoxib was studied in FAP patients because earlier

animal experiments and epidemiologic observations had pointed to an association between regular aspirin use and reduced risk of cancer of the colon and rectum. One recent case-control study of 1201 colon cancer patients in Massachusetts confirmed that regular use of aspirin or other NSAIDs did protect against carcinoma.²⁵ The cases were drawn from tumor registries, while controls were obtained by telephoning adult resident of towns and cities in the state. Regular NSAID use was defined as use at least four days a week for at least a month. Overall, the risk of colon cancer decreased 30% overall, and 40% for Stage II-IV carcinoma in those subjects currently taking NSAIDs.

Prospective studies have been carried out in patients with FAP with non-aspirin non-selective NSAIDs such as sulindac.²⁶ IN 21 FAP patients treated with sulindac 150 mg po BID for three months, colorectal polyps regressed. The number of polyps significantly declined 46% from baseline, while polyps increased by 13% in the placebo patients. The use of non-selective NSAIDs in relatively young patients at high risk for a life-threatening condition has a high- benefit-risk ratio. On the other hand, if chemoprevention of colon cancer in populations at low risk becomes a recommendation, the agent of choice would preferably be an NSAID with less long-term toxicity, like a COX-2 inhibitor. Meanwhile, celecoxib has become the first drug approved to treat FAP, and studies are now ongoing to see if its benefits will extend to prevention of cancer in this patient group.

A startling event has transformed the field of COX-2 research and development. A patent, filed in 1992, for the entire class of COX-2 inhibitors, was awarded on April 18 to the University of Rochester, where researchers discovered the human gene for COX-2 and determined that it had physiologic functions that differed from COX-1.²⁷ The university attorney has concluded that the patent entitles the University of Rochester to royalties on the sales of all COX-2 inhibitors, including the \$1.5 billion in 1999 sales of Celebrex®. The university has filed a lawsuit against Searle and Pfizer, but has begun discussions with both Searle and Merck, the manufacturer of Vioxx®, to negotiate licensing agreements. The most likely immediate result is a protracted series of legal battles, because the stakes are so high. There are precedents for enzyme patents. Because federal support of research grants has decreased over the years, entrepreneurs, institutions and biotech companies have filed patents for previously unpatentable biological entities. The end result may be to increase the cost of drugs and crop seeds, and to slow down basic research where investigators sometimes do not have patent rights to their own discoveries.

3. Denileukin diftitox (Ontak®)

Denileukin diftitox has been approved for treatment of persistent or recurrent T-cell lymphoma whose malignant cells

express the CD25 component of the IL-2 receptor.²⁸ Cutaneous T-Cell lymphoma (CTCL) is a rare skin disease, formerly referred to mycosis fungoides; actually, mycosis fungoides is the most usual presentation of CTCL.²⁸ Only about 1000 new cases of CTCL are diagnosed in the United States each year, so the condition is rare, even for dermatologists to see. Typically, the disease progresses slowly through the years, and may begin as flat, erythematous patches that respond to topical corticosteroid therapy. Symptoms may last for seven years or more prior to diagnosis. In 10-30% of cases, however, the lesions progress to CTCL, and in advanced mycosis fungoides, the patches may become hyperpigmented and pruritic, and tumors or even large-cell lymphoma may develop. Early disease may be treated topically with steroids or mechlorethamine, ultraviolet radiation, or total skin beam electron radiation, often resulting in long remissions. Advanced disease is much more difficult to treat, and conventional chemotherapy has not been very successful. Patients often get infections and can die of sepsis.

Expression of the CD25 component of the T-cell interleukin-2 receptor has been associated with aggressive tumor behavior and shortened survival in CTCL patients.³⁰ Ontak® is a genetically-engineered recombinant fusion protein composed of interleukin-2 amino acid sequences plus diphtheria toxin fragments A and B.³⁰ It binds specifically to the IL-2 receptor on the surface of T-cells, then poisons the malignant T-lymphocytes, as well as some normal lymphocytes, with its attached diphtheria toxin. Here, recombinant DNA technology has manufactured a magic bullet.

This magic bullet is not as specific as its designers may have hoped, although clinical results were promising. FDA approval was based in part on a Phase III study that was carried out in 71 patients with persistent or recurrent CTCL, whose skin biopsies or circulating cells had at least 20% of cells that expressed CD25.²⁸ The patients received a median of six months of therapy, given IV for a 5-day course every 21 days. At the higher dose, 30% of patients showed a 50% or greater reduction in tumor burden. There were seven patients (10%) with complete remissions that lasted a median of nine months. The treatment, however, was not well tolerated. Sixty-nine percent of the patients had an acute hypersensitivity reaction and 91% had a flu-like reaction. Twenty-one per cent were hospitalized for drug-induced effects, most frequently for vascular leak syndrome, fever and dehydration due to GI toxicity. At the current cost of \$10-15,000 for each 5-day course of therapy, the magic bullet may be little more than a research tool at present.

The promise of biologically engineered fusion proteins is that more specific subsets of T-cells can be targeted by improved design of potential binding sites. Preliminary studies have already been done to make bone marrow transplantation

(BMT) less hazardous. Toxins that target the interleukin-2 receptor have been designed to eliminate T-cells from bone marrow grafts that react with host tissue to cause graft-versus-host-disease.³² In mixed mouse and human T-cell cultures, a genetically-engineered form of *Pseudomonas* exotoxin A directed against the IL-2 receptor has completely eliminated CD25 from the cell cultures. When toxin-treated donor marrow was transplanted into mice, GVHD developed in only 10% of the mice compared to 88% of untreated controls. Successful application of the technique to humans undergoing bone marrow transplant would make BMT as accessible as renal transplantation is today.

Well-Publicized Drug Approvals

1. Xenical® (orlistat)

Orlistat is the latest drug to be approved for the treatment of obesity in conjunction with a reduced-calorie diet. It is a reversible lipase inhibitor, preventing the absorption of up to 30% of ingested fat at the recommended dose of 120 mg po three times daily.³³ At a time when increasing obesity is a problem featured in recent headlines, every available modality becomes an option for some individuals.³⁴ In the United States now, 55% of the population is overweight, and one person in four can be considered obese. The idea of a medication that promises that not all ingested calories will be absorbed is a dream for would-be dieters who feel hungry all the time. Such promises have produced so much interest that Xenical® is available at dozens of websites, as well as by conventional prescription. It is indicated for obese individuals whose Body Mass Index (BMI) is 30 or greater (normal 19-25).

The promise works, up to a point. Mean weight loss in the premarketing trials was 12.4 pounds at 6 months and 13.4 pounds after a year of diet and drug.³³ After one year, 57% of treated patients lost >5% of their body weight, compared to 31% of the placebo patients. At the end of two years, these percentages declined to 44% and 24%. There were modest decreases in total cholesterol, LDL-cholesterol and fasting insulin. In obese patients with Type 2 diabetes, marked decreases in LDL- and total cholesterol occurred in patients who achieved greater weight loss.³⁵ During the first year, minor but unpleasant side effects included oily spotting, flatus with discharge and fecal urgency in up to 25% of patients. Fecal incontinence occurred in 7.7%.

Clinicians have pointed out that even minor weight loss in obese patients can have significant effects on blood pressure and serum lipids and decrease the risk of illness. In contrast, health advocates have focused on the ideal case where substantial weight loss or even ideal body weight can be attained by a total change in lifestyle that includes a regular exercise program as well as a sensible, balanced diet. Many individuals who have lost weight have found that it is extremely difficult

to keep it off, so that only a minority can successfully maintain the weight loss. The experience with orlistat reflects this experience, where weight loss essentially stops after six months, and the pounds creep back after the first year. In the clinical trials of orlistat, the overall total loss was only 13 pounds. Many of these people would still have to lose 50-70 pounds to fit in comfortable clothes, bend over to tie their shoes or fit in an airline seat.

In other words, for all except a tenacious few, we do not yet have the technology to treat obesity successfully. The biochemical characteristics that gave our ancestors a survival advantage in times of famine are increasing our risk for illness in times of prosperity.

2. Oseltamivir (Tamiflu®) and Zanamivir (Relenza®)

Both of these neuraminidase inhibitors function by interrupting the replication of both influenza A and influenza B viruses. Both are indicated for treatment of influenza infection, but studies have also shown that they are effective in preventing infection, and approval for this indication is likely.³⁶⁻³⁹ For treatment, both drugs must be started within two days of symptom onset to have any effect. For both, treatment produces a modest decrease in the duration of symptoms, actually less than a day in the case of zanamivir. Both are substantially effective for prophylaxis when used daily throughout the influenza season. Adverse effects for zanamivir, which is administered by oral inhaler BID for five days, include cough and bronchospasm in patients with asthma. Adverse effects for oseltamivir, taken orally BID for five days with food, include nausea in 10% of patients, vomiting and diarrhea. The most serious limitation of the trials completed to this point is the exclusion of elderly or ill subjects, where influenza causes the most morbidity and mortality. There have been no head-to-head trials of these drugs with amantadine or rimantadine for the treatment of influenza A.

Recommendations for populations at risk are that they be vaccinated with influenza virus vaccine prior to each flu season. Preventive administration of oseltamivir for six weeks would cost \$445 for 75 mg daily, about 100 times the drug cost of vaccination, and still will not guarantee coverage because of the unpredictability in the timing of influenza epidemics. There may be some niche indications such as treatment of infection in previously immunized persons, or prevention for patients in nursing homes where breakthrough infections have occurred.

Perspective

■ *How can a practitioner appreciate what real advances and advantages lie under the surface of the jumble of new drug names and new pharmacologic classes that comes tumbling from the FDA every year?*

Very few of the new drugs are commonly prescribed in

ambulatory practice, even after they become better known. Others are used only in specialty practices or medical conditions affecting small numbers of patients. Still others are me-too additions to well-known therapeutic categories with large market potentials. A more practical perspective may become evident by looking at the view from the other end of the telescope: what new agents are available for a particular indication, and how do the new drugs affect existing medical and surgical therapies? Can a new antibiotic decrease length of ICU stay? What are the relative safety profiles of rosiglitazone and pioglitazone, now that troglitazone is no longer available? Drugs make more sense in the evolving context of their particular use in appropriate patients.

■ *How do new drugs fit in the relevant disease treatment guidelines?*

Our use of drugs is becoming more focused and more patient-specific. It is not enough to make sure the patient is compliant with therapy. Pharmacists should encourage patient attainment of recommended goals for blood glucose, blood pressure and cholesterol. New guidelines for pharmacologic and non-pharmacologic management of conditions like hypertension have been published in the medical literature and are now more easily accessible to consumers. Part of the accessibility depends on access to a computer and the Internet, an opportunity that many consumers over the age of 60 have been reluctant to experience. Consumers in this age group often are on multiple medications for chronic health problems. One of the challenges here is to improve patient education in this group.

■ *What are the elements of information that can successfully provide context to balance drug advertisements to consumers and prescribers?*

Pharmacists increasingly have the opportunity to facilitate medication use plans for patients. Access to accurate drug safety and efficacy information is essential for advising patients and prescribers about new drugs. The only information source for some consumers is TV advertising, which could lead viewers to believe that FDA approval is synonymous with an advance in therapy. A balanced view would also warn that new drugs are almost always much more expensive than older alternatives, approval may not include any therapeutic advantage, and everything is not known about the safety of new drugs, as the market withdrawals of bromfenac (Duract®) and troglitazone (Rezulin®) illustrate. The pharmacist is often the only resource to provide a balanced view. Pharmaceutical research has produced some remarkable discoveries, but has also pumped out undistinguished molecular entities calculated only to capture market share. Often the latter have been accompanied by marketing puffery that creates consumer demand. The wisdom to know the difference will profoundly affect patient care.

References - Available on request. ■