Attachment A

ims

February 18, 2009

Senator Jennifer Veiga
Chairperson
Business, Labor and Technology Committee
Colorado State Senate
200 East Colfax
Denver, CO 80203

SUBJECT: Oppose SB 166

Madam Chair and Members of the Committee,

IMS Health is a health information company that provides services to a diverse range of healthcare stakeholders in the public and private sectors in over 100 countries around the world. Our primary interest is in preserving the critical data assets and the *flow of anonymous* data which our nation will need to face the *serious* healthcare challenges ahead, and to continue efforts to improve quality and longevity for our population at an affordable price. We support efforts to protect the privacy of personal health information for patients and applaud your efforts to do so. Our own policies and practices to protect patient privacy include multiple encryption techniques and many overlapping safeguards so that the data we provide to assist healthcare stakeholders in no way allow identification of individual patients.

IMS also understands the need to manage healthcare costs. Collectively, our quality of life depends upon it. We applaud efforts to manage utilization, chronic illnesses, and to increase the appropriate use of generics, which now represents over 70% of all prescribing in this country. We are aware of healthcare reform initiatives, and the complex set of alternatives and possible solutions under consideration at the state and federal levels of our government, such as HIT, universal healthcare, pay for performance and personal accountability. It is our hope that IMS Health data assets will enable this important effort and protect patients by optimizing their care with evidence-based information.

In the context of that necessary debate, it is clear to us is that information will be absolutely necessary to enable these initiatives to succeed. Otherwise, it could be compared to performing surgery while blindfolded. We will make trade-offs without knowledge of the risks and opportunities...and patients care will be compromised.

It is also of great importance to us that the principles that will guide healthcare reform going forward are protected and preserved today. That is why IMS is against data restriction laws which impede the free flow of important information that does not compromise the privacy of individual patients. These legislative proposals undermine the principle of transparency, which is an underlying tenet in healthcare reform, repeatedly expressed by all health experts, agencies and thought-leaders of political parties as well as AARP, SEIU, and a host of consumer advocacy organizations.

IMS HEALTH
660 West Germantown Pike
Plymouth Meeting, PA 19462
USA

Tel: (800) 523-5333
Fax: (800) 523-5333
www.imshealth.com

Legislative efforts to restrict data to specific stakeholders in the healthcare system have been justified over time by a shifting set of rationales, with little if any substance in facts. Initially, they were framed by their proponents in the context of patient and physician privacy to garner support and raise the level of fear around this issue when, in fact, no such risk exists. Today, we hear very little about privacy. Furthermore, two Federal Judges have said there is no privacy issue, supporting our contention that there was intentional exaggeration by some of the proponents of these bills in the first place.

When these arguments failed, it was suggested that these laws would reduce costs. This is a popular theme, but to date there is no information to support such conclusions; and there is significant information to the contrary that suggests marketplace practices already exist to manage cost, without the need for data restrictions that may compromise patient care:

- New Hampshire restricted these data for approximately 9 months in 2006-2007; with no reported impact on costs. If the availability of these data drives costs, how does one account for that?
- The dispensing of new brand medications (products with a market presence of 3 or less years) has declined from 5.7% of total prescriptions dispensed in 2003 to only 1.3% in 2008. At the same time, generic medication grew to represent approximately 70% of dispensed prescriptions in 2008. How would that lead one to conclude that these data were causing physicians to prescribe brand medications inappropriately?
- From 1999 to 2007, the use of prescriber-level data by pharmaceutical research company representatives increased by nearly 56% while the annual rate of prescription drug spend growth plummeted from over 15% to only 1.6%.
- Of particular importance, managed care practices are much more influential in determining what is dispensed. Based on clinical and cost considerations, using active formulary management, patient education, tiered co-pays, and offering patients lower-cost equivalents (generic or brand) when appropriate, managed care continues to lower costs. And they have done so in spite of price increases and a 31% increase in the overall number of prescriptions dispensed from 2003 to 2008.
- Managed Care practices are well established and effective in managing utilization and costs. Today, generic prescribing uptake and share have achieved a national average of 70% of dispensed prescriptions. Once again, how would one conclude that payers in the public or private sectors were being over-run by rampant or irrational prescribing practices?

These laws risk patient care by intentionally impeding the process that brings medical breakthroughs to patients on a timely basis.

- Slowing this process effectively delays treatment. That means patients who can benefit from newer medications may be harmed.
- This law affects all products regardless of patient benefit. Life-saving medications and documented advances will be impacted the same as marginal improvements. At a minimum to protect patients, the legislation should provide for an exception for proven medical breakthroughs (so-called "fast tracked" drugs as determined by the FDA), cancer medications, life-saving therapies, safety warnings from the FDA, etc. No such language exists in the bill.

ims

Proponents of these laws say the medical marketplace will disseminate all the information required for patient care when in fact recent studies published in the *New England Journal of Medicine* showed that patients are not routinely treated according to best practices. Further, the Institute of Medicine indicated that dissemination of proven practices throughout the healthcare system can take as long as 17 years!

In light of these problems and needs, IMS suggests that you are now considering legislation that would remove one of the tools that supports quality improvement and education.

Additionally, legislation restricting these anonymous data risks the health of a robust biotechnology industry.

As members of the bioscience industry attest, these data allow a more efficient process for bringing medical innovation to patients. Without them marketing costs will increase and there will be a need for a relatively larger sales force. This information allows small companies to compete with large companies and fuels the emergent biotech companies that employ small sales forces to reach few physicians...who treat the small populations who may benefit ***(The proverbial needle in a haystack).***

Finally, we object to the idea that government should decide who has access to and use of information. Government deciding to block the flow of information because it wants to control behavior represents a very dangerous precedent.

In conclusion, IMS believes that Senate Bill 166, if enacted, will ultimately hurt patients. We urge you to vote against its passage.

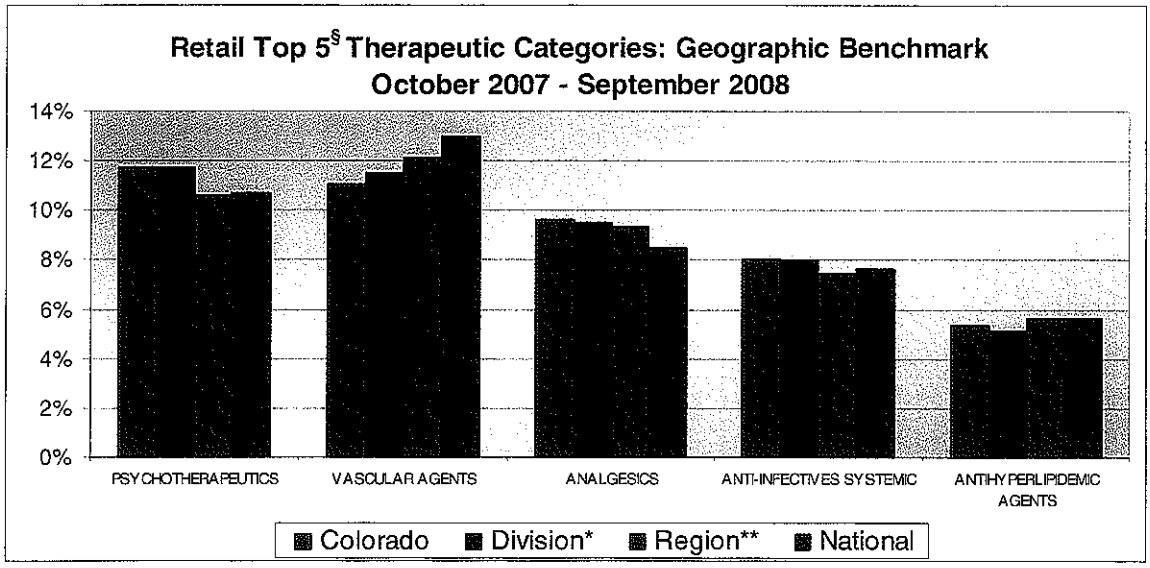
Respectfully submitted,

Randolph Frankel

Randolph Frankel
Vice President, IMS Health

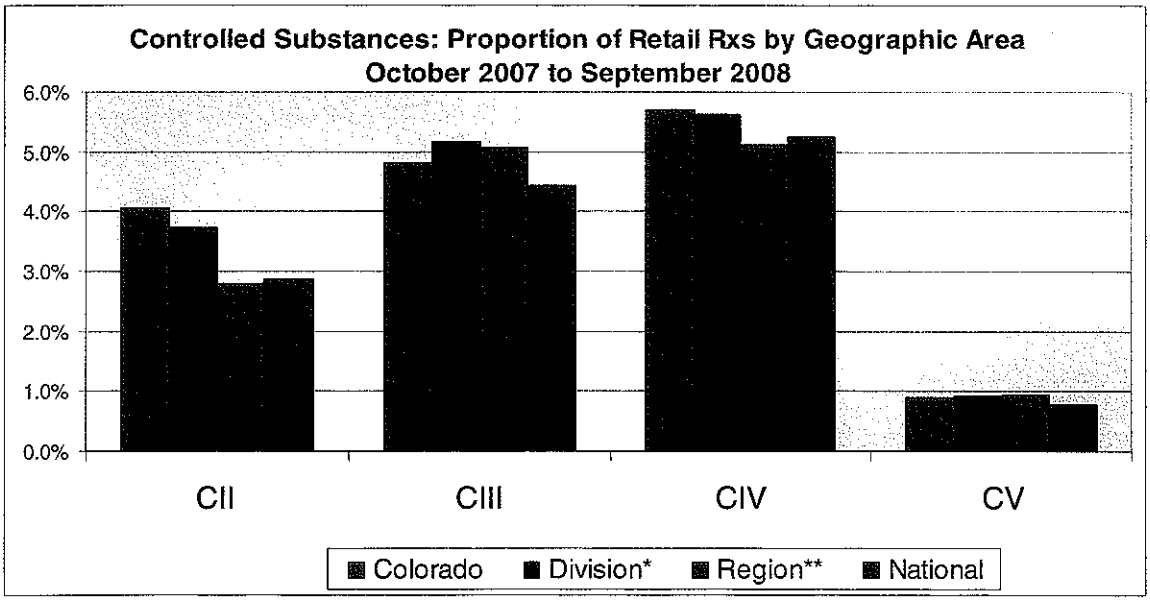
Pharmaceutical Utilization Patterns in Colorado

ims



*Division - Arizona, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming
**Region - Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming
§Top 5 Therapeutic Categories based on Total Retail Filled Prescriptions Oct 2007 to Sep 2008

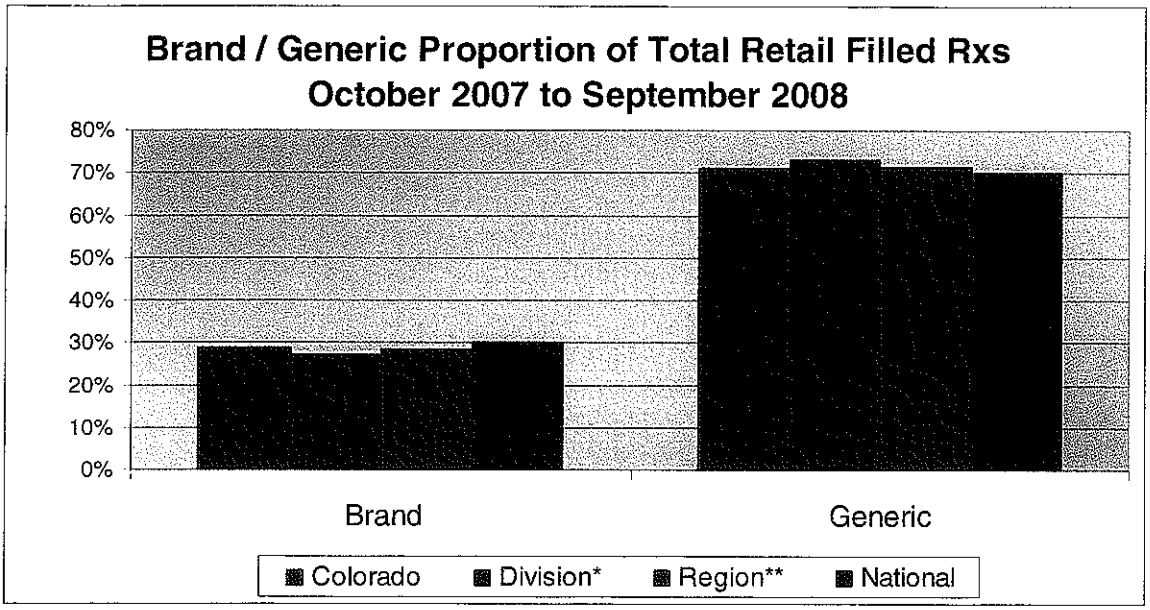
Controlled Substance Utilization Patterns in Colorado



*Division - Arizona, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming
**Region - Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming
§Controlled Substance Utilization based on Total Retail Filled Prescriptions Oct 2007 to Sep 2008

Utilization of Generics in Colorado

ims



* Division - Arizona, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming
** Region - Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming

Brand / Generic Proportion of Total Retail Filled Rxs
October 2007 to September 2008

Rx Type	Colorado	Division*	Region**	National
Brand	10,905,711	40,902,122	167,296,313	990,091,462
Generic	26,998,806	110,203,673	418,995,625	2,308,085,023
Total	37,904,517	151,105,795	586,291,938	3,298,176,485

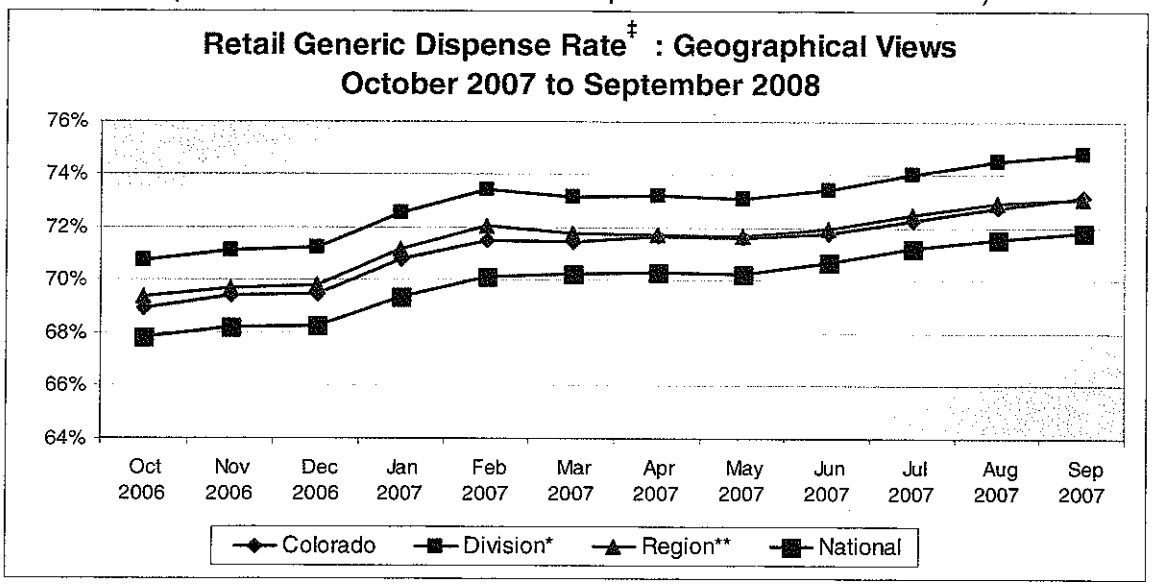
Rx Type Ratio	Colorado	Division*	Region**	National
Brand	**28.8%**	27.1%	28.5%	**30.0%**
Generic	**71.2%**	72.9%	71.5%	**70.0%**

* Division - Arizona, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming
** Region - Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming

Utilization of Generics in Colorado

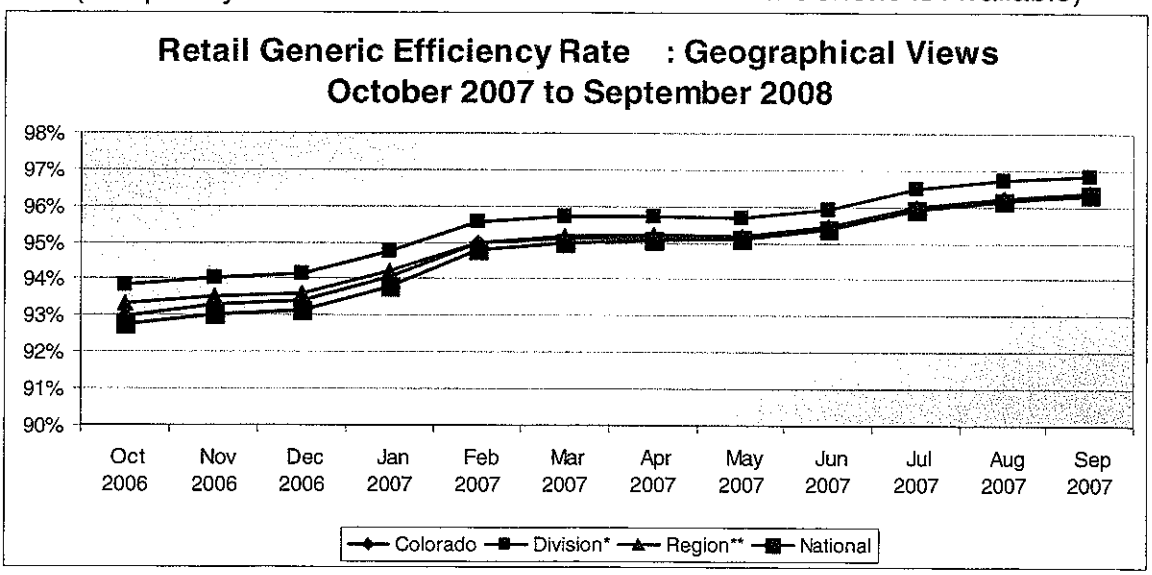
ims

Retail Generic Dispense Rate Over Time
(Percent of Total Retail Prescriptions Filled with Generics)



* Division - Arizona, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming
** Region - Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming

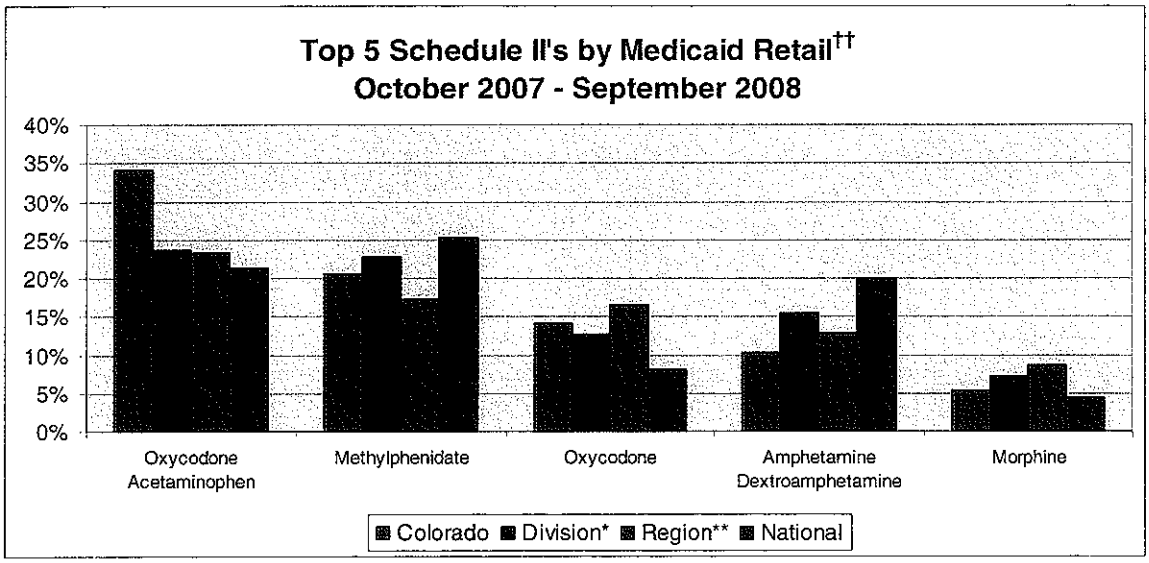
Retail Generic Efficiency Rate Over Time
(Frequency with which a Generic is Used When a Generic is Available)



* Division - Arizona, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming
** Region - Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming

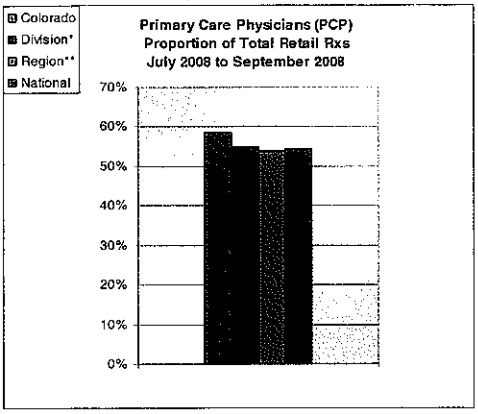
C-II Controlled Substance Utilization in Colorado Medicaid

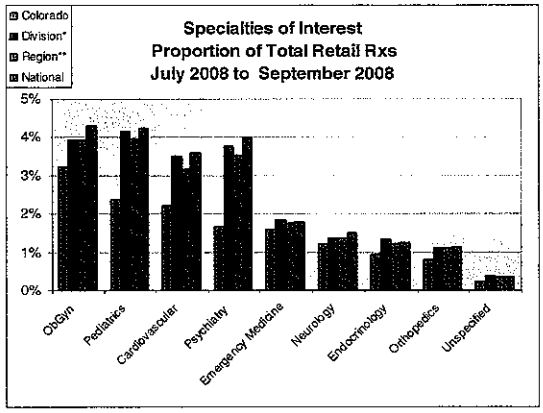
ims



* Division - Arizona, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming
** Region - Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming

Aggregate Prescribing by Specialty in Colorado





* Division - Arizona, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming
** Region - Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming

Specialty Analysis, HIV/AIDS Prescribing in Colorado

ims

Total Retail Prescriptions, Year Ended November 2008

COLORADO	All Prescribers	HIV Therapy Prescribers
	21,020	431
HIV Therapy Prescriber Specialties:	**Prescriber Count**	**Rxs**
Infectious Diseases - IM	23	14,245
Internal Medicine	9	4,444
Nurse Practitioner	4	1,952
Family Medicine	3	1,542
Internal Medicine - Pediatrics	1	936
Unspecified	1	827
Family Practice	2	611
Physician Assistant	1	446
Nuclear Medicine	1	179
Diagnostic Radiology	1	141
Prescribers Responsible for 80% of HIV/AIDS Rxs	**46**	25,323

Specialty Analysis, Alzheimer's Disease Prescribing in Colorado

Total Retail Prescriptions, Year Ended November 2008

COLORADO	All Prescribers	Alzheimer's Prescribers
	21,020	2,798
Alzheimer's Prescriber Specialties:	**Prescriber Count**	**Rxs**
Internal Medicine	251	25,656
Family Medicine	251	19,070
Neurology	73	14,832
Family Practice	69	6,132
Internal Medicine - Geriatric Medicine	23	4,574
Psychiatry	30	3,039
Physician Assistant	27	2,347
Nurse Practitioner	29	2,141
Family Practice - Geriatric Medicine	6	2,026
General Practice	10	1,044
Internal Medicine - Pediatrics	4	398
Child and Adolescent Psychiatry	3	369
Pulmonary Disease	2	333
Infectious Diseases - IM	3	274
Psychiatry/Neurology	1	211
General Surgery	1	184
Licensed Practical Nurse	1	166
Child Neurology	2	163
Gastroenterology	3	160
Endocrinology	2	135
Unspecified	2	130
Forensic Psychiatry	1	108
Hospitalist	1	104
Physical Medicine and Rehab	1	82
Ophthalmology	2	81
Nuclear Medicine	1	53
Diagnostic Radiology	1	44
Prescribers Writing 80% of Alzheimer's Rxs	**800**	83,856

Prescription Drug Spending Trends In The United States: Looking Beyond The Turning Point

The drug spending trends observed in the 1980s, 1990s, and the first few years of this decade have changed dramatically in the past five years—bringing both opportunity and threat.

by Murray Aitken, Ernst R. Berndt, and David M. Cutler

ABSTRACT: Annual growth in real prescription drug spending averaged 9.9 percent during 1997–2007 but has slowed since 2003, falling to 1.6 percent in 2007. More patent expirations, increased generic penetration, and reduced new product innovations have contributed to this turning point. We document trends and identify underlying components: declines in the role of blockbuster drugs, increased importance of biologics and vaccines relative to traditional pharmaceuticals, and a changing medication mix away from those prescribed principally by primary care physicians toward those mostly prescribed by specialists. We conclude with policy implications. [*Health Affairs* 28, no. 1 (2009): w151–w160 (published online 16 December 2008; 10.1377/hlthaff.28.1.w151)]

ADJUSTED FOR INFLATION, U.S. SPENDING ON prescription drugs grew 9.9 percent annually between 1997 and 2007—tripling in total real spending.[1] Since 2003, however, growth rates have declined rapidly, and in 2007 spending grew but 1.6 percent—the slowest since 1974, the only decline on record (Exhibit 1).

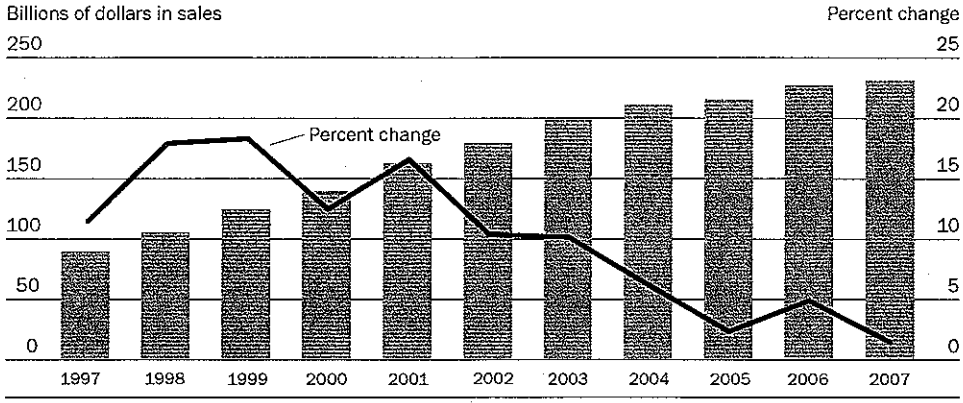
Although comparable 2007 national data on other health-sector spending are not yet available, prescription drug spending growth is likely to be lower than any other major medical care sector. Whereas prescription drug costs were once the bane of payers, that concern has now been replaced by worries about hospital care, imaging, and professional services.[2]

What accounts for the decline in the growth of overall drug spending? Do re-

Murray Aitken is senior vice president, Healthcare Insight, at IMS Health in Norwalk, Connecticut. Ernst Berndt (eberndt@mit.edu) is the Louis E. Seley Professor in Applied Economics, Alfred P. Sloan School of Management, at the Massachusetts Institute of Technology in Cambridge. David Cutler is a professor of economics at Harvard University in Cambridge.

DOI 10.1377/hlthaff.28.1.w151

EXHIBIT 1
Size And Growth Of The U.S. Retail Pharmaceutical Market, 1997–2007



SOURCE: IMS Health, National Sales Perspectives, December 2007 (sales deflated by implicit gross domestic product deflator, $2000).
NOTES: Dollar figures (bars) relate to the left-hand *y* axis. Percent change (line) relates to the right-hand *y* axis.

cent trends suggest a new era of low growth? What are the policy implications of the turning point? We explore these issues here. Our data come from the National Sales Perspectives (NSP), which audits sales of pharmaceutical products from wholesalers to pharmacies and other outlets, and the National Prescription Audit (NPA), which tracks prescriptions dispensed by pharmacists; both are produced by IMS Health.

Components Underlying Changing Trends In Prescription Drug Sales

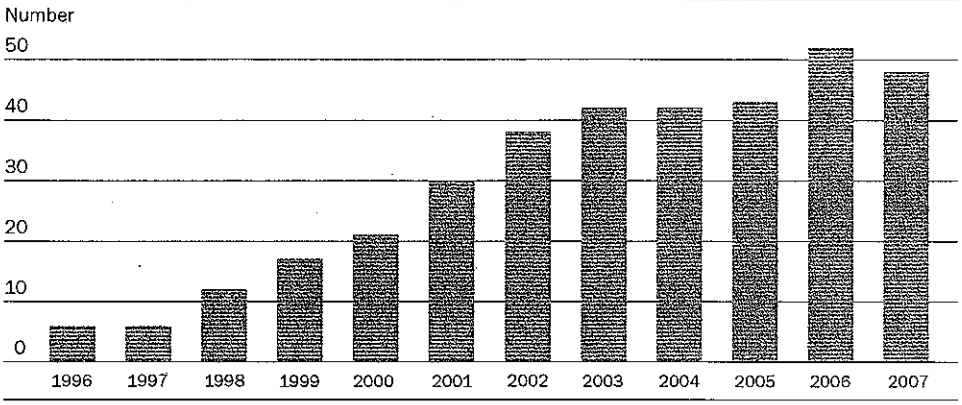
Underlying the trends in overall drug sales are several dynamics driven by changes in "blockbuster" drugs; shifts in the mix of medications between primary care and specialist drugs; and changes in the mix among traditional chemical-based pharmaceuticals, biologics, and vaccines.

■ **Blockbuster drugs.** The number of blockbuster drugs—those selling in excess of $1 billion (real 2000 dollars) in the United States—increased more than eightfold between 1997 and 2006, from six to fifty-two (Exhibit 2).[3] Concomitantly, spending on blockbusters increased from about 12 percent of all sales in 1996 to almost half of all sales in 2006, accounting for three-quarters of prescription drug spending growth over the same time period.

In 2007, for the first time, the number of billion-dollar products fell—from fifty-two to forty-eight—and their share of all sales also fell slightly, to 44 percent. As more blockbusters go off patent and fewer new ones are developed, the share of sales attributable to blockbuster molecules will likely decline still further.

■ **Primary care and specialist drugs.** A marked change has occurred in the mix of medications away from those prescribed principally by primary care physicians

EXHIBIT 2
Number Of Blockbuster Drugs, 1996–2007



SOURCE: IMS Health, Market Insights Analysis, December 2007.
NOTE: Blockbuster drugs are those exceeding $1 billion in sales per year in 2000 dollars.

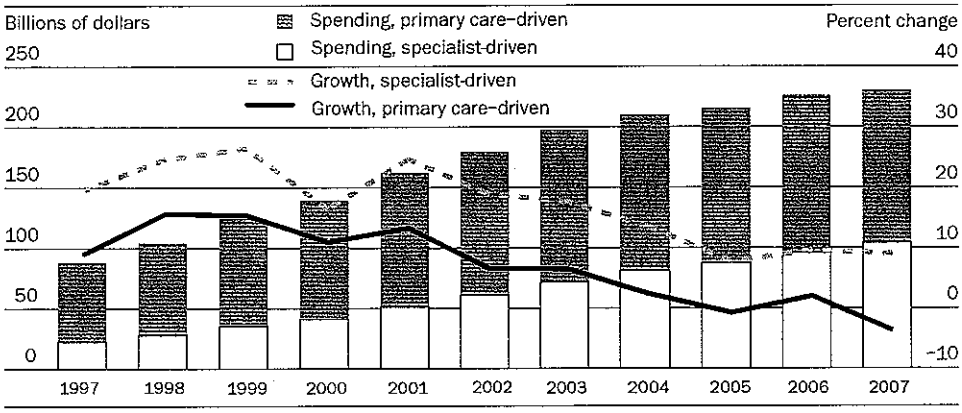
and toward those prescribed mostly by specialists.[4] In 2007, the five leading primary care–driven therapeutic classes (by dollars) were the lipid regulators, acid pump inhibitors, respiratory agents, antidepressants, and oral antidiabetics. Together they accounted for 22 percent of drug spending. Primary care drugs as a whole accounted for 55 percent of all sales. Leading specialist drug therapeutic classes included oncologics, antipsychotics, anti-epileptics, erythropoetins, and autoimmune agents. These five categories accounted for 20 percent of all drug spending, while specialist drugs as a whole accounted for 45 percent.

Notably, real spending growth in primary care–driven drugs fell steadily between 2003 and 2005, from 6.4 percent in 2003 to –0.8 percent in 2005, increasing temporarily to 1.9 percent in 2006, but then declining by 3.7 percent in 2007 (Exhibit 3). In sharp contrast, specialist-driven real drug spending grew 17.5 percent in 2003, slowed to 7.7 percent in 2005 and then rebounded to 9.5 percent in 2006 and 8.9 percent in 2007. The reduction in overall prescription drug sales growth is therefore due entirely to slower growth and even declines in sales of primary care drug classes.

■ **Pharmaceuticals, biologics, and vaccines.** Changes are also apparent in the mix among traditional pharmaceuticals, biologics, and vaccines. Traditional pharmaceuticals are "small molecule" drugs, in contrast to larger-protein biologics (defined as medications manufactured via recombinant DNA technology) and vaccines. The most significant biologic molecules are oncologics; they are significant for their targeted approach to slowing cancer progression and for their high cost of treatment: According to IMS Health data, Avastin (colorectal cancer) cost on average $42,960, Herceptin (breast cancer) cost $27,990, and Tykerb (breast cancer) cost $16,575 per course of treatment in 2007.

The price of oncologics has been increasing over time. The most expensive drug

EXHIBIT 3
Size And Growth Of The U.S. Primary Care–Driven And Specialist-Driven Prescribing Markets, 1997–2007



SOURCE: IMS Health, National Sales Perspectives, December 2007 (sales deflated by implicit gross domestic product deflator, $2000).
NOTES: Dollar figures (bars) relate to the left-hand *y* axis. Percent change (lines) relates to the right-hand *y* axis.

in the early 1990s was Taxol (used for treating breast cancer), which sold for $4,000 per year. The cost of Avastin today is ten times higher.

Vaccines, once a neglected sector, have recently become much more important. Prevnar, a conjugate pneumococcal vaccine, and Gardasil, for prevention of cervical cancer, are the first two blockbuster vaccines, with the current private-sector price being $84 and $125 per dose, respectively, for the three-dose regimen.[5]

The decomposition among pharmaceuticals, biologics, and vaccines corresponds as well to drugs that are mostly self-administered (small-molecule pharmaceutical tablets and capsules) versus therapies primarily administered by health care providers (biologics and vaccines, injected or infused).

Between 2002 and 2007, real spending on biologics grew at an average annual rate of 16 percent, while vaccine spending grew 19.3 percent annually. In comparison, sales of traditional small-molecule drugs grew only 3.7 percent annually. Overall, biologics' share of the market rose from 9 percent in 2002 to 15 percent in 2007, while vaccine sales grew from less than 1 percent in 2002 to 2 percent in 2007. Molecule types are also related to the specialty of the prescribing physician. Almost all biologics are prescribed by specialists and a sizable portion of spending in specialty-driven biologics is for oncology products. Thus, the growth of biologics and the shift to specialty-physician therapies are intimately related.

Causes Of Change

Underlying these trends in sales are dramatic changes in pharmaceutical innovation, along with a transformed market environment.

■ **Pharmaceutical innovation.** Despite remarkable advances in our under-

standing of biology and genetics over the past decade, recent years have seen a marked decline in the number of new molecular entities (NMEs) approved by the Food and Drug Administration (FDA). According to the FDA, between 1999 and 2001 the average total number of such new product approvals was about thirty-five per year (six biologics and twenty-nine pharmaceuticals), whereas between 2005 and 2007 this number fell to about twenty (three biologics and seventeen pharmaceuticals).

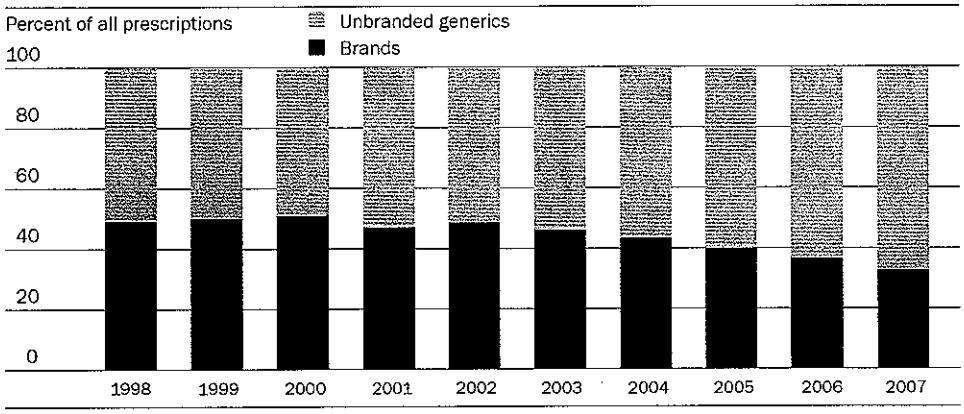
With smaller numbers of new product approvals, the vintage composition of drugs sold has matured and has become increasingly vulnerable to generic entry. Based on IMS Health NPS data, we calculate that products introduced within the prior five years accounted for 34 percent of total drug sales in 1999. That share has declined steadily since then, to just 19 percent of total sales in 2007. Meanwhile, the value of brand-name products at risk of same-molecule generic penetration has almost doubled, from an average of about $9 billion per year between 2002 and 2005 to about $16 billion in 2006–07. The list of drugs losing patent protection in recent years has been substantial: Norvasc (value: $2.6 billion), Lotrel ($1.5 billion), and Flonase ($1.2 billion). Moreover, drugs likely to come off patent protection soon include Cozaar in 2010; Lipitor, Plavix, and Seroquel in 2011; and Diovan, Viagra, and Evista in 2012.

■ **The changing environment for sales.** Drugs having patent protection and extensive market power continue to command high prices. But in therapy classes where there are multiple treatment options, competition has increased—across branded molecules, and between branded and generics. Employers and the pharmaceutical benefit management (PBM) firms with which they contract have increasingly moved to more sophisticated formularies in an effort to limit spending. IMS NPA data indicate that a typical formulary now charges $6 for generic medications, $29 for preferred branded drugs, and $40 or more for nonpreferred branded drugs. This tier structure creates enormous incentives for consumers to take generic medications. Medicare Part D has contributed to this trend, with most plans having at least three-tier copayment formularies and many having a fourth tier incorporating sizable coinsurance payments. All told, the generic share of total prescriptions increased from 51 percent in 2002 to 67 percent in 2007 (Exhibit 4).

Even within Medicare Part D's short history, the total retail prescription volume share dispensed as generic has steadily increased, from 59 percent in January 2006 to 68 percent in December 2007. Generic penetration has also become more rapid. According to IMS NPS data, in 2002 branded products retained 28 percent of their prescription volume twelve months after patent expiry. In 2007 that figure dropped to 14 percent.

The increased extent and speed of generic penetration has resulted in substantial cost savings for purchasers. The daily cost of drug therapy across all products in that class fell 32 percent for lipid regulators in the year after generic entry, 32 percent for bisphosphonates, 42 percent for selective serotonin reuptake inhibi-

EXHIBIT 4
Brand-Name And Generic Drugs' Share Of Total Retail Dispensed Prescription Drugs, 1998–2007



SOURCE: IMS Health, National Prescription Audit, December 2007.

tors (SSRIs), and 20 percent for calcium-channel blockers.

To quantify the expenditure impact of increased generic penetration, we simulated spending if the generic efficiency rate (for all molecules for which a generic version is available, the proportion of units dispensed as generics) had stayed at its actual 2003 rate (77.3 percent) instead of increasing to 86.4 percent, which it did by 2007.[6] Cumulative pharmaceutical spending would have been 13.5 percent greater (22 percent higher in 2007 alone).

■ **Statins and Lipitor: overturning conventional wisdom.** It has long been conventional wisdom that after a drug loses patent protection and generic entry occurs, the total branded plus unbranded number of prescriptions/extended units for the same molecule decreases, mainly because promotional spending by the brand-name company drops around the time of patent expiration.[7] For the first time in recent history, this conventional wisdom has been overturned by cholesterol-lowering "statin" drugs.

No pharmaceutical shows dramatic changes in the market better than Lipitor, the best-selling statin from Pfizer. Lipitor was the ultimate blockbuster. At its peak in 2006, it had an average price of $2.79 per day and generated $8.6 billion in U.S. sales ($13.6 billion internationally).

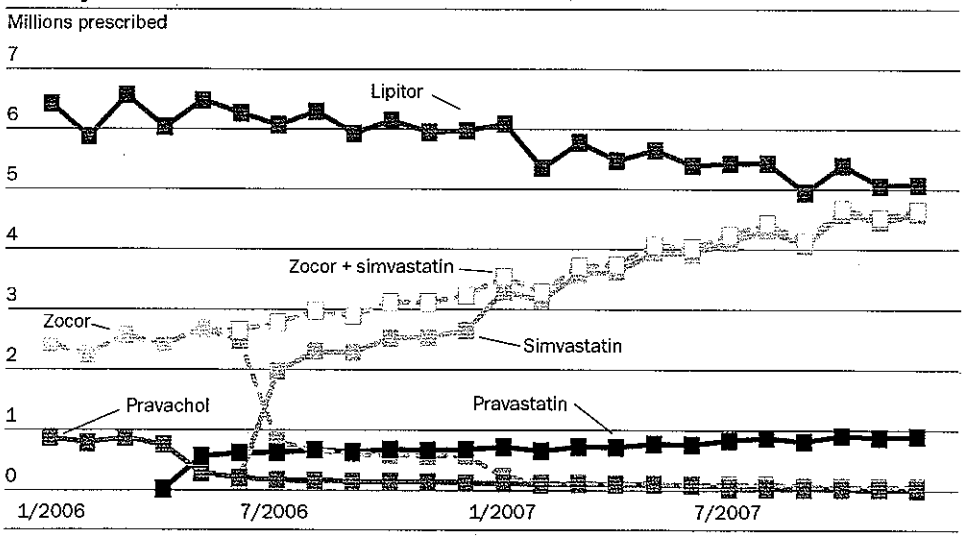
Lipitor is but one statin drug. The second leading seller was Zocor, an earlier entrant. Zocor (generic: simvastatin) lost patent protection and faced generic competition beginning 23 June 2006. As a result of provisions of the Hatch-Waxman Act known as Paragraph IV certifications as well as subsequent judicial rulings against Merck (the manufacturer of Zocor), the generic company Teva was awarded exclusive rights to market the 10 mg, 20 mg, and 40 mg versions of simvastatin for 180 days after Merck's patent expiration. Similarly, Ranbaxy ob-

tained exclusive rights to market the 80 mg version. On its own, Merck reached an agreement in early 2006 with the generic firm Dr. Reddy to produce an "authorized generic" in all strength versions following Zocor's loss of patent protection.[8] Although a limited amount of generic simvastatin entry occurred after 23 June 2006, unfettered generic entry occurred 180 days later, in late December 2006. Other statins have gone off patent as well. Mevacor (lovastatin) lost its patent protection in 2001, and Pravachol (pravastatin) went off patent 25 April 2006. Generic versions of both came out rapidly thereafter.

Although some controversy still exists, general consensus among the medical community is that for most patients, the various statins are equally effective and safe, and thus are therapeutically substitutable. An exception is at very high dosages, where Lipitor is believed to be more effective.[9] Since brand-name Lipitor was still patent-protected in early 2007, whereas much less costly generic versions of Pravachol (pravastatin) and Zocor (simvastatin) were now on the market, payers, insurers, and PBMs were given incentives to switch patients on Lipitor to pravastatin or simvastatin. This typically took the form of moving Lipitor to the highest copayment tier and placing the two generics in the lowest tier.

For Pravachol and generic pravastatin, the total brand plus generic number of prescriptions since loss of patent protection increased only slightly (Exhibit 5). After Zocor lost patent protection, however, total monthly Zocor plus generic simvastatin prescriptions boomed, from 2.8 million in June 2006 to 4.8 million in December 2007. Sales of prescription Zocor plummeted, but those of generic

EXHIBIT 5
Monthly Prescribing Trends In The Statin Therapeutic Class, Brand-Name And Generic, January 2006–December 2007



SOURCE: IMS Health, National Prescription Audit, December 2007.

simvastatin grew dramatically.

The new sales have come directly from previous Lipitor users or people who would have started on Lipitor. In 2007 the number of prescriptions of Lipitor fell 12 percent, including 26 percent in new starts. Sales of Lipitor have declined the most at lower dosages—10 mg and 20 mg per day—and have held steady only for 80 mg doses. Between 2006 and 2007, domestic sales of Lipitor fell 6.5 percent below 2006 levels. The Lipitor experience is the first instance in which generic versions of one molecule have substituted so significantly for brand-name versions of a different molecule.

Policy Implications

These changing trends and their underlying causes have several implications for policy. First, they are consistent with the view that for payers and consumers, the health spending prospects are more optimistic than many fear. Costs of prescription pharmaceuticals—an important segment of health care—are rising very slowly or even falling. Unless the situation changes unexpectedly in the near future, this trend will continue. Current projections have not taken this reduced spending growth into account. For example, the Centers for Medicare and Medicaid Services (CMS) recently projected 8.5 percent pharmaceutical spending growth in 2006, 6.7 percent in 2007, 6.8 percent in 2008, and an average annual growth rate of 8.2 percent between 2006 and 2017.[10] Our data suggest that these forecasts are too high.

Second, the converse of this implies difficult times for the pharmaceutical industry, particularly for traditional small-molecule manufacturers. Expected future revenue is one factor affecting pharmaceutical research and development (R&D) and innovation.[11] Slow sales growth is likely to put pressure on research budgets and marketing costs and to create incentives for mergers. The existence of fewer, larger entities with tighter research budgets may stifle or limit investment in innovation and the ongoing prospects for improved therapeutics' reaching the market. Unless biopharmaceutical R&D productivity improves or results in an increased proportion of "blockbuster" molecules affecting large populations (the latter an unlikely outcome, given recent trends), reduced revenues are likely to constrain future rates of new product innovation.

Third, our simulation results document that sizable cost savings can be attained by increasing generic efficiency rates; greater use of generics when available since 2003 has resulted in 22 percent lower pharmaceutical spending in 2007. More generally, our results suggest that the design of drug cost sharing is extremely important. For the large number of drugs for which there is competition across branded molecules, and especially between branded and generic drugs, out-of-pocket costs have a major influence on what patients consume, and perhaps on their health outcomes.[12] Used judiciously, cost-sharing instruments can be employed by governments, PBMs, and private payers in future attempts to limit

"Is the reduction in new blockbusters the result of technological wells running dry, or the implication of increased regulation?"

growth in pharmaceutical spending.

A major exception to this rule may be drugs that have extensive market power in therapeutic segments where not taking the medication can result in death. In such segments—oncology in particular—recent launch prices have been high and increasing over time. Pressures to address such costs will increase, but governments do not have competition as an effective response lever. This has led some policy analysts to recommend that in those situations, Medicare should establish a temporary administered-price mechanism.[13] How Medicare can best deal with the pricing of truly unique and innovative life-saving new drugs is likely to become an issue generating considerable controversy.

Fourth, our results are likely to increase pressures placed on agencies such as the FDA. Is the reduction in new blockbusters the result of technological wells running dry, or the implication of increased regulatory stringency? Should the FDA be doing something about this, or has it done all it should or can do? Should industry focus on "niche busters" rather than "blockbusters," searching for more stratified medicines?[14] These questions have always lingered in the background of pharmaceutical policy, and they may soon come to the forefront.

Fifth, the focus in the past few years on reducing rates of growth of drug spending is now coinciding with the loss of exclusivity for a substantial portion of that spending. This suggests that further efforts to limit the uptake of new therapies through extension of formulary design to tier four, switching to coinsurance rather than copayments, or reducing the effective period of exclusivity for products might not be necessary. Moreover, the long-term impacts of these measures on both the cost and the quality of health outcomes remain unknown.

What is clear, however, is that the prescription drug spending trends observed in the 1980s, 1990s, and the first few years of this decade have changed dramatically in the past five years, and that when one looks beyond the recent turning point, the growth, size, and composition of prescription drug spending is likely to be dramatically different, raising both policy opportunities and dangers.

Ernst Berndt acknowledges research support from the Merck Pharmaceutical Policy Program; David Cutler, from the National Institute on Aging.

NOTES

1. All inflation adjustments use the gross domestic product (GDP) deflator.
2. Mark E. Miller, executive director, Medicare Payment Advisory Commission, "MedPAC Recommendations on Imaging Services," Statement before the House Ways and Means Subcommittee on Health, 17 March 2005, http://www.medpac.gov/publications/congressional_testimony/031705_TestimonyImaging-Hou.pdf (accessed 15 August 2008).
3. Statistics are sometimes presented using nominal data—the number of drugs with sales of more than a billion dollars using prices from that year. By this metric, the increase in blockbusters was tenfold—six to sixty.
4. This classification is based on prescription shares by prescriber type, not dollar shares.
5. Centers for Disease Control and Prevention, "CDC Vaccine Price List," updated 8 October 2008, http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm (accessed 4 November 2008).
6. We assume an unchanged actual market size in units and unchanged actual brand-generic average prices per extended unit (tablet, capsule, and so on).
7. R. Caves, M. Whinston, and M. Hurwitz, "Patent Expiration, Entry, and Competition in the U.S. Pharmaceutical Industry," *Brookings Papers on Economic Activity* 1 (1991): 1–48; E. Berndt, I. Cockburn, and Z. Griliches, "Pharmaceutical Innovations and Market Dynamics: Tracking Effects on Price Indexes for Antidepressant Drugs," *Brookings Papers on Economic Activity: Microeconomic* 2 (1996): 133–188; and E. Berndt, M. Kyle, and D. Ling, "The Long Shadow of Patent Expiration: Generic Entry and Rx-to-OTC Switches," in *Scanner Data and Price Indexes*, ed. R. Feenstra and M. Shapiro (Chicago: University of Chicago Press, 2003), 229–267.
8. On authorized generics and Paragraph IV certifications, see E.R. Berndt et al., "Authorized Generic Drugs, Price Competition, and Consumers' Welfare," *Health Affairs* 26, no. 3 (2007): 790–799. Information regarding authorized generics for Zocor is found in "Recent Key Generic Launches—A Focus on Zocor," *RxWatch* (Summer 2006): 1.
9. P. Jones et al., "Comparative Dose Efficacy Study of Atorvastatin versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin in Patients with Hypercholesterolemia (the CURVES Study)," *American Journal of Cardiology* 81, no. 5 (1998): 582–587; and "Drug Comparisons—HMG-CoA Reductase Inhibitors," *Drug Digest*, 2007, http://www.drugdigest.org/DD/PrintablePages/Comparisons/1,20038,37-15,00.html (accessed 4 November 2008).
10. See Exhibit 2 in S. Keehan et al., "Health Spending Projections through 2017: The Baby-Boom Generation Is Coming to Medicare," *Health Affairs* 27, no. 2 (2008): w145–w155 (published online 26 February 2008; 10.1377/hlthaff.27.1.w145); A. Catlin et al., "National Health Spending in 2006: A Year of Change for Prescription Drugs," *Health Affairs* 27, no. 1 (2008): 14–29; and Congressional Budget Office, *The Long-Term Outlook for Health Care Spending*, Pub. no. 3085 (Washington: CBO, November 2007).
11. D. Acemoglu and J. Linn, "Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry," *Quarterly Journal of Economics* 119, no. 3 (2004): 1049–1090.
12. D. Goldman, G. Joyce, and Y. Zheng, "Prescription Drug Cost Sharing: Associations with Medication and Medical Utilization and Spending and Health," *Journal of the American Medical Association* 298, no. 1 (2007): 61–69.
13. R. Frank and J. Newhouse, "Mending the Medicare Prescription Drug Benefit: Improving Consumer Choices and Restructuring Purchasing," Hamilton Project Discussion Paper no. 2007-03 (Washington: Brookings Institution, April 2007).
14. M.R. Trusheim, E.R. Berndt, and F.L. Douglas, "Stratified Medicine: Strategic and Economic Implications of Combining Drugs and Clinical Biomarkers," *Nature Reviews: Drug Discovery* 6, no. 4 (2007): 287–293.

IMS Health Information in Medical and Academic Research

The provision of information and support to researchers has been a longstanding practice of IMS Health. Over the last year, the company has launched a Professional and Academic Affairs group in order to work with these key constituencies in a more focused and structured manner.

As a result, IMS currently has over 100 research projects underway or in the development queue. The nature of these studies is varied, but they all involve compelling economic and vital public health subjects. These include the safety of antidepressants in adolescents, the use of gastrointestinal drugs in children, evolving colorectal cancer treatment patterns, the impact of evidence-based practices in hypertension, the popular acceptance of new treatments and technologies, treatment variability in gastroenterology, patterns of chance in prescribing related to heart disease and the economic impact of erectile dysfunction drugs.

IMS Health Information for Doctors and Organized Medicine

Additionally, IMS works with a number of medical societies and specialty associations to help their leadership and members better understand the pharmaceutical marketplace. IMS provides content for American Medical Association's *Therapeutic Insights*, a continuing education publication for doctors. The company also collaborates with the leadership of medical associations, for example, to help them better understand and describe patterns of use of antibiotics and controlled substances, and to evaluate the effectiveness of educational interventions. IMS also provides these organizations with comparative views of phenomena such as payor dynamics, the effects of Medicare Part D and changes in treatment patterns.

Bibliography of Recent Publications

IMS information is a key component in hundreds of scholarly papers and articles in peer-reviewed journals. Below is a list of selected publications from 2004-07 that have relied upon IMS Health's data:

Allen-Ramey FC; Bukstein D; Luskin A; Sajjan SG; Markson LE. "Administrative claims analysis of asthma-related health care utilization for patients who received inhaled corticosteroids with either montelukast or salmeterol as combination therapy." J Manag Care Pharm. 2006; 12(4):310-21

Arellano F, Wentworth CE, Arana A, Fernandez C, Paul C. "Risk of Lymphoma Following Exposure to Calcineurin Inhibitors and Topical Steroids in Patients with Atopic Dermatitis." Journal of Investigative Dermatology, 9 November 2006

Arellano FM, Ulcickas Yood M, Wentworth CE, Oliveria SA, Rivero E, Verma A, Rothman KJ. "Use of Cyclo-Oxygenase 2 Inhibitors (COX-2) and Prescription Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) in UK and USA Populations. Implications for COX-2 cardiovascular profile." Pharmacoepidemiology and Drug Safety 2006;15:861-872.

Bahls C, "Special Focus: Migraine," American College of Physicians Observer, June 2005, 10-11.

Black L, Naslund MJ, Gilbert TD Jr, Davis EA, Ollendorf DA. "An Examination of Treatment Patterns and Costs of Care Among Patients with Benign Prostatic Hyperplasia." The American Journal of Managed Care 2006;12(4):S99-S110.

Blazer D G, Hybels C F, Fillenbaum, G G, Pieper C F, "Predictors of Antidepressant Use Among Older Adults: Have They Changed Over Time?" American Journal of Psychiatry, April 2005, 705-710.

Brassard P; Kezouh A; Suissa S. "Antirheumatic drugs and the risk of tuberculosis." Clin Infect Dis. 2006; 43(6):717-22

Colman E, "Anorectics on Trial: A Half Century of Federal Regulation of Prescription Appetite Suppressants," Annals of Internal Medicine, September 6, 2005, 380-385.

Condon T P, National Institute on Drug Abuse, "Drug Abuse in the 21st Century - What Problems Lie Ahead for the Baby Boomers?" National Institutes of Health, Department of Health and Human Services, September 16, 2004.

Cook A, "Testosterone therapy: The answer for aging men?" Mayo Clinic Health Information, July 12, 2004.

Danzon P M with Wang Y R and Wang L, "The Impact of Price Regulation on the Launch Delay of New Drugs," Health Economics, September 2004, 269-292.

Eisenberg SS. "Building the case for asthma as a disease management program." Disease Manag. 2004; 7(3):202-15

Fenter TC; Runken MC; Black L; Eaddy M. "Finasteride versus dutasteride: a real-world economic evaluation." Am J Manag Care. 2007; 13 Suppl 1:S23-8

Fischer M A, Schneeweiss S, Avorn J, and Solomon D H, "Medicaid Prior-Authorization Programs and the Use of Cyclooxygenase-2 Inhibitors," NEJM, November 18, 2004, 2187-2194.

Fisher Wilson J, "Cheaper Drugs in Foreign Markets Increase The Focus on Domestic Drug Prices," Annals of Internal Medicine, April 2004, 677-680.

Garnett WR; Gilbert TD; O'Connor P. "Patterns of care, outcomes, and direct health plan costs of antiepileptic therapy: a pharmacoeconomic analysis of the available carbamazepine formulations." Clinical Ther. 2005; 27(7):1092-103

Gianfrancesco F; Rajagopalan K; Goldberg JF; Wang RH "Hospitalization risks in the treatment of bipolar disorder: comparison of antipsychotic medications." Bipolar Disord. 2007; 9(3):252-61

Gilbert TD, Smith D, Ollendorf DA. "Patterns of Use, Dosing, and Economic Impact of Biologic Agent Use in Patients with Rheumatoid Arthritis: A Retrospective Cohort Study." BMC Musculoskeletal Disorders 2004;5:36.

Goodman J C, "Drug Reimportation: The Free Trade Solution," National Center for Policy Analysis, February 16, 2005.

Guda N M, Vakil N, "Proton pump inhibitors and the time trends for esophageal dilation," Am J Gastroenterol, May 2004, 797-800.

Hawkins R G, Houston M C, "Population-wide diuretic use directly associated with the incidence of end-stage renal disease in the United States? A hypothesis," Am J Hypertens, June 18, 2005, 744-749.

Hoffman JM, Shah ND, Vermeulen LC, Hunkler RJ, Hontz KM "Projecting future drug expenditures - 2004," American Journal of HealthSystem Pharmacy, January 15, 2004, 145-158.

Hoffman JM, Shah ND, Vermeulen LC, Hunkler RJ, Hontz KM "Projecting future drug expenditures - 2005," American Journal of HealthSystem Pharmacy, January 15, 2005, 149-167.

Hoffman JM, Shah ND, Vermeulen LC, Schumock GT, Grim P, Hunkler RJ, Hontz KM "Projecting future drug expenditures - 2006," American Journal of HealthSystem Pharmacy, January 15, 2006, 123-138.

Hoffman JM, Shah ND, Vermeulen LC, Schumock GT, Grim P, Hunkler RJ, Hontz KM "Projecting future drug expenditures - 2007," American Journal of HealthSystem Pharmacy, February 1, 2007, 298-314.

Hopkins Tanne J, "US doctors and patients are split on approval of generic thyroid hormone," British Medical Journal, July 24, 2004, 329.

Issa MM; Runken MC; Grogg AL; Shah MB Emory. "A large retrospective analysis of acute urinary retention and prostate-related surgery in BPH patients treated with 5-alpha reductase inhibitors: dutasteride versus finasteride." Am J Manag Care. 2007; 13 Suppl 1:S10-6

Jick SS; Jick H. "Cerebral venous sinus thrombosis in users of four hormonal contraceptives: levonorgestrel-containing oral contraceptives, norgestimate-containing oral contraceptives, desogestrel-containing oral contraceptives and the contraceptive patch." Contraception. 2006; 74(4):290-2

Jick SS; Jick H. "The contraceptive patch in relation to ischemic stroke and acute myocardial infarction." Pharmacotherapy. 2007; 27(2):218-20

Jick SS; Kaye JA; Russmann S; Jick H. "Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 microg of ethinyl estradiol." Contraception. 2006; 73(3):223-8.

Joyce AT, Harrison DJ, Loebel AD, Carter CT, Ollendorf DA. "Effect of Initial Ziprasidone Dose on Length of Therapy in Schizophrenia." Schizophrenia Research 2006;83(2-3):285-292.

Joyce AT, Harrison DJ, Loebel AD, Ollendorf DA. "Impact of Atypical Antipsychotics on Outcomes of Care in Schizophrenia." The American Journal of Managed Care 2005;11(8):S254-S261.

Joyce AT, Iacoviello JM, Nag S, Sajjan S, Jilinskaia E, Throop D, Pedan A, Ollendorf DA, Alexander CM. "End Stage Renal Disease-Associated Managed Care Costs Among Patients With and Without Diabetes." Diabetes Care 2004;27:2829-2835.

Jumadilova Z, Varadharajan S, Girase P, Ollendorf DA. "Retrospective Evaluation of Outcomes in Patients with Overactive Bladder Receiving Tolterodine Versus Oxybutynin." American Society of Health-System Pharmacists, 2006;63:2357-2364.

Keating KN; Friedman HS; Perfetto EM. "Moxifloxacin versus levofloxacin for treatment of acute rhinosinusitis: a retrospective database analysis of treatment duration, outcomes, and charges." Curr Med Res Opin. 2006; 22(2):327-33

Kuntze, MD, Daniel A. Ollendorf, MPH "Reduced Mortality Rate after Intensive Statin Therapy in Managed-care Patients.", Value In Health, 2007; 10:2,:161-169

Lee PP; Levin LA; Walt JG; Chiang TH; Doyle JJ; Stern LS; Dolgitser M "The impact of glaucoma coding in a large claims database." American Journal of Ophthalmology. 2007; 143(5):867-70

Lee WC; Arcona S; Thomas SK; Wang Q; Hoffmann MS; Pashos CL. "Effect of comorbidities on medical care use and cost among refractory patients with partial seizure disorder." Epilepsy Behav. 2005; 7(1):123-6

Lee WC; Hoffmann MS; Arcona S; D'Souza J; Wang Q; Pashos CL. "A cost comparison of alternative regimens for treatment-refractory partial seizure disorder: an econometric analysis." Clin. Ther. 2005; 27(10):1629-38

Leslie L K,Newman T B, Chesney P J, Perrin J M, "The Food and Drug Administration's Deliberations on Antidepressant Use in Pediatric Patients," Pediatrics, July 2005, 195.

MacDougall C, Powell J P, Johnson C K, Edmond M B, Polk R E, "Hospital and community fluoroquinolone use and resistance in Staphylococcus aureus and Escherichia coli in 17 US hospitals," Clin Infect Dis, August 14, 2005, 435-40.

MacDougall DA; Feliu AL; Boccuzzi SJ; Lin J "Economic burden of deep-vein thrombosis, pulmonary embolism, and post thrombotic syndrome.: Am J Health Syst Pharm. 2006: 63 (20 Suppl 6):S5-15

McLaughlin T; Geissler EC; Wan GJ. "Comorbidities and associated treatment charges in patients with anxiety disorders." Pharmacotherapy. 2003;23(10):1251-6

McLaughlin TP; Khandker RK; Kruzikas DT; Tummala R. "Overlap of anxiety and depression in a managed care population: Prevalence and association with resource utilization." J Clin Psychiatry, 2006; 67(8):1187-93

Naslund M; Black L; Eaddy M; Batiste LR "Differences in alpha blocker usage among enlarged prostate patients receiving combination therapy with 5 ARIs." Am J Manag Care. 2007; 13 Suppl 1:S17-22

Oberholzer-Gee F and Noorein Inamdar S, "Merck's Recall of Rofecoxib — A Strategic Perspective," NEJM, November 2005, 97-105.

Ollendorf D, Joyce A, Rucker M. "Rate of New-Onset Diabetes Among Patients Treated With Atypical or Conventional Antipsychotic Medications for Schizophrenia". Medscape General Medicine, 2004;6:1-12.

Ollendorf DA, Lidsky L. "Infliximab Drug and Infusion Costs Among Patients with Crohn's Disease in a Commercially-Insured Setting." American Journal of Therapeutics 2006;13:502-506.

Ollendorf DA, Massarotti E, Birbara C., Burgess S. "Frequency, Predictors, and Economic Impact of Upward Dose Adjustment of Infliximab in Managed Care Patients with Rheumatoid Arthritis." Journal of Managed Care Pharmacy 2005;11(5):383-393.

Packer C, Stevens A, Cook A, Raftery J, "Diffusion of thromboysis for acute myocardial infraction from 1981 to 2000 In England: trend analysis and comparison with need," International Journal of Tech Assess Health Care, September 2004, 531-536.

Perfetto EM; Subedi P; Jumadilova Z. "Treatment of overactive bladder: a model comparing extended-release formulations of tolterodine and oxybutynin." Am J Manag Care. 2005; 11(4 Suppl):S150-7

Prescott JD; Factor S; Pill M; Levi GW. "Descriptive analysis of the direct medical costs of multiple sclerosis in 2004 using administrative claims in a large nationwide database." J Manag Care Pharm. 2007; 13(1):44-52

Rajagopalan R; Iyer S; Perez A. "Comparison of pioglitazone with other antidiabetic drugs for associated incidence of liver failure: no evidence of increased risk of liver failure with pioglitazone." Diabetes Obes Metab. 2005; 7(2):161-9

Rajagopalan R; Rosenson RS; Fernandes AW; Khan M; Murray FT. "Association between congestive heart failure and hospitalization in patients with type 2 diabetes mellitus receiving treatment with insulin or pioglitazone: a retrospective data analysis. Clinical Ther. 2004; 26(9):1400-10

Rubin L C, "Merchandising Madness: Pills, Promises, and Better Living Through Chemistry," Journal of Popular Culture, November 2004, 369.

Rules and Regulations, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products - Part 2 of 3, Federal Register, January 24, 2006.

Schatz M; Leibman C. "Inhaled corticosteroid use and outcomes in pregnancy." Ann Allergy Asthma Immunol. 2005; 95(3):234-8

Seftel AD, Sun P, Swindle R. "The Prevalence of Hypertension, Hyperlipidemia, Diabetes Mellitus and Depression among Men with Erectile Dysfunction." Journal of Urology 2004;171:2341-2345.

Stafford R S, "National Trends in Osteoporosis Visits," Archives of Internal Medicine, July 26, 2004, 1525 - 1530.

Stafford R S, Furberg C D, Finkelstein S N, Cockburn I M, Alehegn T, Ma J, "Impact of Clinical Trail Results on National Trends of Alpha Blockers Prescribing Trends, 1996-2002," JAMA, January 2004, 54-62.

Stahl S M, "A rash proposal for psychopharmacologists treating bipolar disorder: become an amateur dermatologist," Clinical Psychiatry News, June 2005, 6.

Statins Don't Increase Breast Carcinoma Risk, Study Says," NCI Cancer Bulletin, May 11, 2004.

Stempel DA; McLaughlin TP; Stanford RH. "Treatment patterns for pediatric asthma prior to and after emergency department events." Pediatr Pulmonol. 2005; 40(4):310-5

"Study Links High Testosterone and Prostate Cancer Link" NCI Cancer Bulletin, May 18, 2004, 1-2.

"Study: Doctors Limited in Rx Training", CASA Publications, July 7, 2005.

Suissa S; Bernatsky S; Hudson M. "Antirheumatic drug use and the risk of acute myocardial infarction." Arthritis Rheum. 2006; 55(4):531-6

Suissa S; Hudson M; Ernst P. "Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis." Arthritis Rheum. 2006; 54(5):1435-9

Varadharajan S, Jumadilova Z, Girase P, Ollendorf DA. "Economic Impact of Extended-Release Tolterodine Versus Immediate- and Extended-Release Oxybutynin Among Commercially-Insured Persons with Overactive Bladder." The American Journal of Managed Care 2005;11(6):S140-S149.

Wilensky J, Fiscella RG, Carlson A M, Morris L S, Walt J, "Measurement of persistence and adherence to regimens of IOP-lowering glaucoma medications using pharmacy claims data," Am J Ophthalmo, January 2006, 28-33.

Wingard J R, Wood C A, Sullivan E, Berger M L, Gerth W C, Mansley E C, "Caspofungin versus amphotericin B for candidemia: a pharmacoecomomic analysis," Clin Ther, June 2005, 960-969.

Xinghua Hu S, Foster T, Kieffaber A, "Pharmacogenomics and personalized medicine: mapping of future value creation," Biotechniques, September 2005, 1-6

Yazdani C; McLaughlin T; Smeeding JE; Walt J. "Prevalence of treated dry eye disease in a managed care population." Clin Ther. 2001;23(10):1672-82

Therapeutic Insights

Diagnosis and Management of Migraine in Adults

In cooperation with the Connecticut State Medical Society

January, 2007

AMA Therapeutic Insights is a quarterly Continuing Medical Education (CME) newsletter intended to provide primary care physicians with evidence-based guidelines for selected medical conditions. This CME activity will serve as a clinical context for your review of personalized physician prescribing reports that you can request after each issue. These reports are for your use only and are intended to improve clinical practice and prescribing habits as a function of self-assessments. To review your confidential personalized prescribing data, go to www.ama-assn.org/go/therapeuticinsights

Disclosures
For faculty disclosures, see page 12.

Webpage
Therapeutic Insights is available online at www.ama-assn.org/go/therapeuticinsights

Expiration date: January, 2008

WELCOME to the AMA Therapeutic Insight's quarterly online newsletter. This CME program is intended for primary care physicians and those physicians who care for patients experiencing migraine headaches. Upon completion of this activity, participants should be able to:

- *Increase awareness of the prevalence of migraine in the general population*
- *Encourage screening and diagnosis of migraine*
- *Promote an evidence-based approach to treatment and management*

The American Medical Association is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AMA designates this educational activity for a maximum of 1 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity. Non-physicians may receive a certificate of participation for completing this activity. It is estimated that it will require one hour to review this material and answer the self-assessment questions. Record your answers to the evaluation and self-assessment questions online at www.ama-assn.org/go/therapeuticinsights or by completing the answer sheet at the end of this newsletter and faxing or mailing according to instructions.

Statement of Need

Migraine affects approximately 12% of the US adult population and is associated with diminished quality of life, significant functional impairment, curtailed activities, and absence from work and school. It is underdiagnosed, undertreated, and frequently misdiagnosed. Migraine should be considered a chronic disease rather than a series of recurrent headache attacks and is significantly associated with physical and psychiatric comorbidities. Thus, migraine treatment must take into account a patient's overall health status. This CME activity has been designed to help clinicians to recognize, diagnose, and treat migraine to reduce migraine-related disability.

Migraine is Highly Prevalent Among the United States Population

A common and disabling primary headache disorder, migraine exerts such a sufficient impact on those who suffer from it that the World Health Organization (WHO) ranks it 19th among diseases that result in disability.[1] It is estimated that approximately 18% of women and 6% of men in the United States suffer from migraine,[2,3] or roughly 12% of adults. Migraine is significantly more prevalent among Caucasian women (20.4%) than among African- (16.2%) or Asian- (9.2%) American women. Similarly, 8.6%, 7.2%, and 4.2% of Caucasian men, and African- and Asian-American men, respectively, are reported to experience migraine.[4] Migraine prevalence varies by age and gender, as shown in Figure 1.

Results of a study that quantified the prevalence and burden of migraine in the United States reveal that 91% of patients with migraine experience headache-associated functional impairment and 53% experience headaches that cause them to curtail activities or go to bed. Although proportions of men and women reporting disability were similar, women reported greater duration of migraine-associated restriction in activity, compared with men. Migraine is also associated with lost work days, reduced school and work productivity, and disruption in household work productivity.[2]

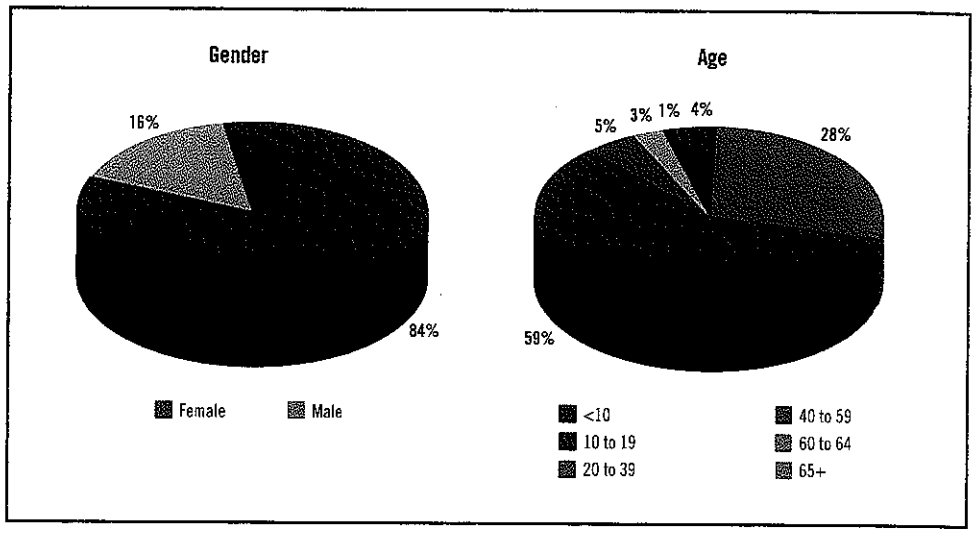


Figure 1. Migraine Prevalence by Age and Gender Derived from Prescription-generated Data
Source: IMS Health

Underdiagnosis and Misdiagnosis are Common

Migraine is underdiagnosed, undertreated, and frequently misdiagnosed. A recent retrospective analysis of prescription drug claims data from 6.2 million continuous health plan enrollees in 2003 revealed the following:[5]

- Only 3% of the enrolled population,[5] compared with an estimated national prevalence of 12%,[2,3] received a diagnosis of migraine, which suggests that some patients with migraine may have received a misdiagnosis of nonmigraine headache or did not seek diagnosis of their headaches[5]
- Of patients with a diagnosis of migraine, only 50% received a prescription[5]
- Of those who received a prescription[5]
  - 59% received narcotics/opioids, which are not indicated for treatment of migraine
  - Only 41% of diagnosed patients received a prescription for a migraine-specific triptan

These findings are consistent with those of a national medical claims data base that show that fewer than 40% of patients receive a prescription (Figure 2) and, of those, slightly more than half are given a migraine-specific triptan (Figure 3). These data do not, however, account for the self-medication with nonprescription drugs.

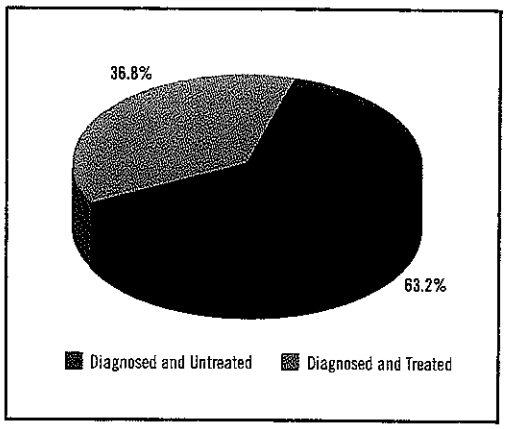


Figure 2. Patients with Migraine Diagnosed and Treated vs. Patients with Migraine Diagnosed and Untreated
Source: PharMetrics

Migraine is frequently misdiagnosed as sinus headache

In 1978, a widely read lay publication about headache first called attention to the observation that many cases of "sinus headache" may actually be migraine.[6] Nonetheless, Americans continue to consider "sinus headache" to be a headache diagnosis, even though there is little evidence in the medical literature that acute sinus disease is a common cause of headache.[7] The reason for confusion may be clear: migraine headache can be associated with facial pain as well as with nasal congestion and rhinorrhea.[7,8] It is not associated with the more typical purulent nasal discharge and pathologic radiologic findings of acute sinusitis.[8] The authors of a study published in 2004

conclude that 88% of patients with a history or medical diagnosis of "sinus" headache have experienced migraine.[8] These results are consistent with those of a survey of published clinical studies in which nearly 90% of participants with self-diagnosed or physician-diagnosed sinus headache met International Headache Society (IHS) criteria for migraine-type headache. It thus appears likely that most individuals who bring recurrent "sinus headaches" to the attention of physicians suffer instead from migraine.[7]

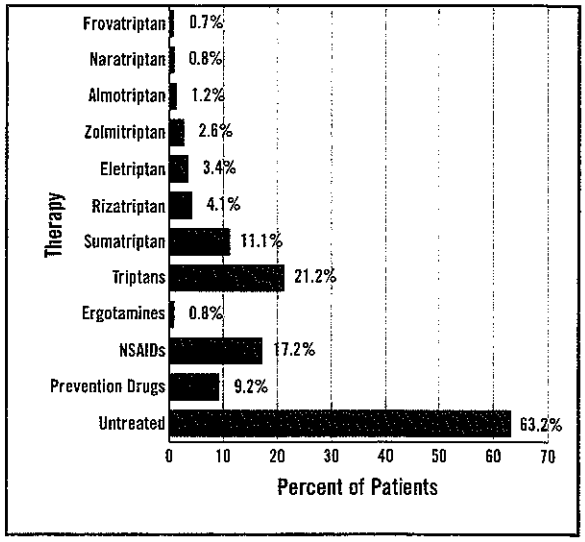


Figure 3. Use of Indicated Medications in the Treatment of Migraine
Source: PharMetrics

Migraine is a Complex Neurologic Phenomenon

Current theories on the cause of migraine headaches, with or without aura, point to a neurogenic mechanism, involving the trigeminal vascular system as a common pathway for headache pain. Migraine headache may be comprised of 5 phases: prodrome, aura, headache, resolution, and postdrome. Not all are necessary or occur in individual patients. Prodrome is the occurrence of preheadache symptomatology that signals the awareness that the headache of migraine is impending. These symptoms may consist of subtle premonitory signs that develop hours to days prior to onset of headache. Aura, which can be visual or somatosensory, can herald the onset of pain but occurs in only about 15% of attacks. It is not a necessary component of migraine. Headache typically follows aura and prodrome and may be unilateral or bilateral, and typically becomes moderate to severe in intensity. Migraine sufferers may be photo- and phonophobic and may experience nausea, vomiting, and decrease in appetite. Resolution and postdrome are characterized as relief of headache pain and a period of migraine symptomatology that persists after resolution, respectively.[9,10]

Screening and Diagnosis

Screening

Patients may not complain of headache unless asked about it, and women who may have menstrual migraine or menstrually associated migraine may believe that headaches are a normal part of the reproductive cycle. An easy-to-administer three-question screen can help to identify patients who may have migraine.[11,12]

In the primary care setting, the 3-item ID Migraine™ migraine screener, which includes one disability question and 2 symptom questions offers 81% sensitivity and 75% specificity relative to an IHS-based migraine diagnosis, with a positive predictive value of 93%.[12] In the primary care validation study for ID Migraine, patients had to have headaches that interfered with their ability to work, study or enjoy life or had to want to talk to the physician about their headache. These pre-screening questions elevated the base rate of migraine in the study population resulting in the very high positive predictive value. Definitive diagnosis of migraine requires the exclusion of secondary headaches as noted below.

3-Item ID Migraine™ migraine screener[12]

1. Has a headache limited your activities for one or more days during the last three months? __Yes __No
2. Are you nauseated or sick to your stomach when you have a headache? __Yes __No
3. Does light bother you when you have a headache? __Yes __No

Positive responses to 2 of 3 questions suggest a diagnosis of migraine.

Diagnosis

While the migraine screening questions may suggest that the patient has a migraine, the diagnosis is based on the IHS criteria. Approach to a patient with suspected migraine should include careful history with particular emphasis on headaches during the previous 6 months, focused physical and neurologic examination, and use of a headache diary to document frequency, duration, pattern of headache, pain intensity, and potential triggers.[13] Secondary causes of headache need to be ruled out, such as those due to tumors, subdural hematomas, infection and other serious conditions. The SNOOP-T[15] approach to headache red flags can assist in identifying worrisome headaches.

Results of a recent study support a diagnosis of migraine in patients with episodic, disabling primary headaches who have an otherwise normal physical exam.[14]

Worrisome Headache: Red Flags —"SNOOP-T"[15]

SYSTEMIC SYMPTOMS (fever, weight loss) or SECONDARY RISK FACTORS (HIV, systemic cancer)
NEUROLOGIC SYMPTOMS or abnormal signs (confusion, impaired alertness or consciousness)
ONSET: sudden, abrupt, or split-second
OLDER: new onset and progressive headache, especially in middle age >50 yr (giant cell arteritis)
PREVIOUS HEADACHE HISTORY: first headache or different (change in frequency, severity, or clinical features
TRIGGERED HEADACHE: by Valsalva activity, exertion, or sexual intercourse

Criteria for Migraine Without and With Aura (ICHD-2)

Migraine without aura

Description: Recurrent disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea an/or photophobia or phonophobia.

Diagnostic Criteria:

A. At least 5 attacks fulfilling B-D

B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

C. Headache has at least two of the following characteristics:
   1. unilateral location
   2. pulsating quality
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity (*eg,* walking or climbing stairs)

D. During headache at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia

E. Not attributed to another disorder

Migraine with aura

Description: Recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5-20 minutes and last for less than 60 minutes. Headache with features of migraine without aura usually follows the aura symptoms. Less commonly, headache lacks migrainous features or is completely absent.

Diagnostic criteria: (Typical aura with migraine headache)

A. At least 2 attacks fulfilling criterion B-D

B. Aura consisting of at least one of the following, but no motor weakness:
   1. fully reversible visual symptoms including positive features (*eg,* flickering lights, spots or lines) and/or negative features (*ie,* loss of vision)
   2. fully reversible sensory symptoms including positive features (*ie,* pins and needles) and/or negative features (*ie,* numbness)
   3. fully reversible dysphasic speech disturbance

C. At least 2 of the following:
   1. homonymous visual symptoms and/or unilateral sensory symptoms
   2. at least one aura symptom develops gradually over 5 minutes and/or different aura symptoms occur in succession over 5 minutes
   3. each symptom lasts 5 minutes and 60 minutes.

D. Headache fulfilling criteria B-D for migraine without aura begins during aura or follows aura within 60 minutes

E. Not attributable to another disorder

From Headache Classification Subcommittee of the International Headache Society. International Classification of Headache Disorders, 2nd ed. Cephalalgia. 2004;24 (Suppl 1):150.

The ICHD-2 now recognizes menstrual and menstrually-associated migraine. Pure menstrual migraine is defined as migraine in a menstruating woman that fulfill criteria for migraine without aura; attacks occur exclusively on days 1 ± 2 (*ie*, days -2 to +3) of menstruation in at least 2 out of 3 menstrual cycles and at no other times of the cycle. Menstrually-related migraine is defined as migraine attacks in a menstruating woman that fulfill criteria for migraine without aura, that occur on days 1 ± 2 (*ie*, days -2 to +3) of menstruation in at least 2 out of 3 menstrual cycles *and additionally at other times of the cycle*.[1]

Migraine comorbidity

Migraine is consistently associated with depression, anxiety, and bipolar disorders[17] as well as with somatic illness. A recent survey conducted by IMS Health noted that anxiety, gastrointestinal disorders, essential tremor, stroke, mitral valve prolapse, allergy, asthma, and irritable bowel syndrome exhibit comorbidity with migraine, as shown in Figure 4. These data are based on medical diagnosis and are thus subject to Berkson bias.

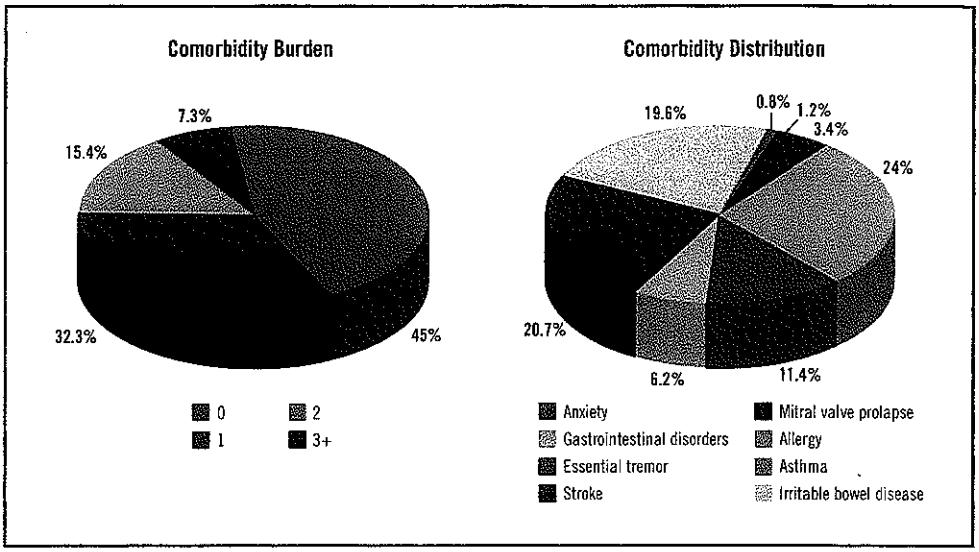


Figure 4. Comorbidities in Migraine Patients
Source: PharMetrics

Although results of a recent, large prospective study[18] of apparently healthy women 45 years of age demonstrated that any history of migraine was associated with increased risk of major cardiovascular disease, the risk varied according to aura status. Compared with women with negative migraine history, women with active migraine with aura exhibited significantly increased risk of major cardiovascular events, ischemic stroke, myocardial infarction, coronary revascularization, angina, and death resulting from ischemic CVD after a mean follow-up period of 10 years. Women with active migraine without aura, however, did not exhibit significantly increased risk for any ischemic vascular event.[18] A recent epidemiologic study that examined somatic and psychiatric comorbidity in the general population noted comorbidity between migraine and allergy/allergic reaction, gastrointestinal complaints, musculoskeletal complaints, other neurological diseases, skin and subcutis disorders, female genital complaints, and neoplasms as well as with depression, anxiety, and other mental disorders.[19]

Migraine Treatment

After establishing the diagnosis, treatment should incorporate avoidance of potential migraine triggers and risk factors, including avoidance of excessive caffeine intake; lifestyle modification that includes regular exercise, regular sleep and wake schedules, and regular meals; acute therapy, and prophylactic therapy, if indicated, and regularly scheduled medical follow-up. Given the potential for episodic migraine to transform into chronic migraine, its associated comorbidities, and duration of disease that typically spans decades, migraine should be managed as a chronic disease with episodic occurrences rather than as isolated headache attacks.

Migraine is treated primarily by family practice and internal medicine physicians, and by other specialties as shown in figure 5.

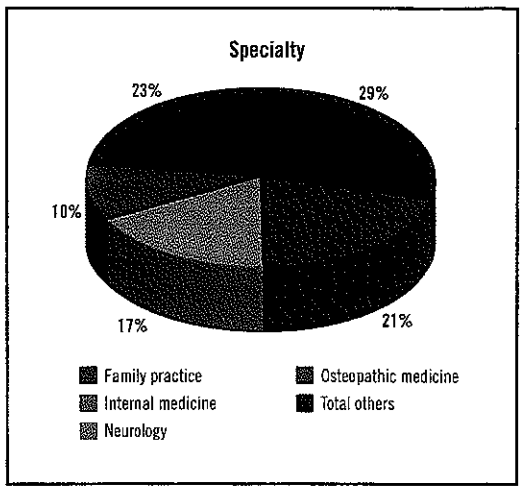


Figure 5. Treatment of Migraine Patients by Medical Specialty
Source: IMS Health

Acute therapy

It is important to remember, however, that by the time patients consult a physician for migraine, they may have tried a variety of OTC medications with less-than-satisfactory results. It is critical to question patients about potential analgesic overuse, which can be associated with rebound headache and chronic daily headache.[20-22]

For acute treatment physician and patient must make a series of decisions:

1. Should acute treatment be changed?
2. Oral vs non-oral therapy
3. Triptan vs nontriptan therapy
4. How to optimize benefits of treatment

Migraine treatment should rapidly relieve pain and associated symptoms (within 2 hours) without disturbing side effects. If treatment does not do so it should be changed.

In general, acute treatments are most effective when given early in a migraine attack, while pain is still mild. If acute treatment does not deliver the expected benefits, it may be helpful to treat earlier in the attack, increase the dose, or change the route of administration. For some patients, combining a triptan with a nonsteroidal anti-inflammatory drug (NSAID) can be highly effective.[23] Migraine attacks that are mild or escalate gradually can, in some individuals, be aborted with over-the-counter (OTC) analgesics such as aspirin and acetaminophen, combination products that contain aspirin/acetaminophen/caffeine, or NSAIDs such as ibuprofen, and naproxen.

The decision for oral vs other routes of administration is multifactorial. Most patients prefer oral treatment, but other routes should be considered for those who do not respond to oral agents and for those whose headaches are of very rapid onset. In addition, nonoral treatments may be useful for patients with prominent nausea and vomiting.

The choice of triptan vs nontriptan treatment depends upon the severity of pain and headache-related disability. Patients who report disability—in the absence of such contraindications as uncontrolled hypertension—may benefit from triptans. Dihydroergotamine mesylate (Migranal) nasal spray and ergotamine/caffeine combinations may also be used on an acute basis (Table 1).[24] Migraine-specific triptans are now considered first-line therapy and their activity is due to their interaction with serotonin receptors.

Table 1. Agents Used for Acute Therapy of Migraine[24-26]

Generic (Brand)	Dosage Forms	Weight of Evidence
Sumatriptan (Imitrex)	25, 50, 100 mg tabs 5, 20 mg nasal spray 4.6 mg auto-injection 6 mg vial	A
Zolmitriptan (Zomig)	2.5, 5 mg tabs 2.5, 5 mg ODT*	A
Rizatriptan (Maxalt)	5, 10 mg tabs 5, 10 mg ODT*	A
Naratriptan (Amerge)	1, 2.5 mg tabs	A
Almotriptan (Axert)	6.25, 12.5 mg tabs	A**
Frovatriptan (Frova)	2.5 mg tab	A**
Eletriptan (Relpax)	20, 40 mg tabs	A**
Dihydroergotamine mesylate (Migranal Nasal Spray)	4 mg/mL in glass vial	A
Ergotamine/caffeine (Cafergot, Wigraine)	1 mg ergotamine 100 mg caffeine tabs Cafergot suppositories: 2 mg ergotamine, 100 mg caffeine	B

Highest available tablet strength is the starting dose for all triptans for most adults.

*ODT—orally disintegrating tablet (offers no advantage in the speed of onset; can be taken without water when water is not available or if hard to swallow due to nausea.

**Almotriptan, frovatriptan and eletriptan were approved for acute migraine treatment after publication of AAN guidelines.

Strength of evidence (quality of evidence)

Grade A. Multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings.

Grade B. Some evidence from randomized clinical trials supported the recommendation, but the scientific support was not optimal. For instance, few randomized trials existed, the trials that did exist were somewhat inconsistent, or the trials were not directly relevant to the recommendation. An example of the last point would be the case where trials were conducted using a study group that differed from the target group of the recommendation.

The triptans are similar to one another in their mechanism of action, acting only on serotonin receptors, but they differ among themselves with respect to onset of action and half-life. All are available in tablet formulations. Naratriptan[27] and frovatriptan[28] have longer half-lives than the other 5 triptans, but their onset of action is generally slower. Zolmitriptan[29] and sumatriptan[30] are available in nasal spray formulations which are characterized by rapid onset of action; they can be useful in patients with nausea. Sumatriptan[30] is also available for self-injection. Triptan medications are generally well tolerated; they should not be used in patients with uncontrolled hypertension.[27-33]

Figures 6 and 7 show triptan prescriptions filled in Connecticut and nationally. These data should not be interpreted to suggest that one triptan is therapeutically superior to another, but merely reflect the current environment of prescribing these agents.

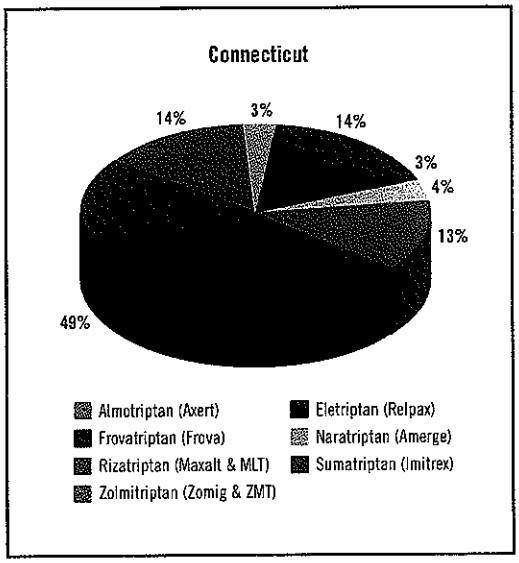


Figure 6. Triptan Prescriptions Dispensed at Retail Pharmacies in Connecticut
Source: IMS Health

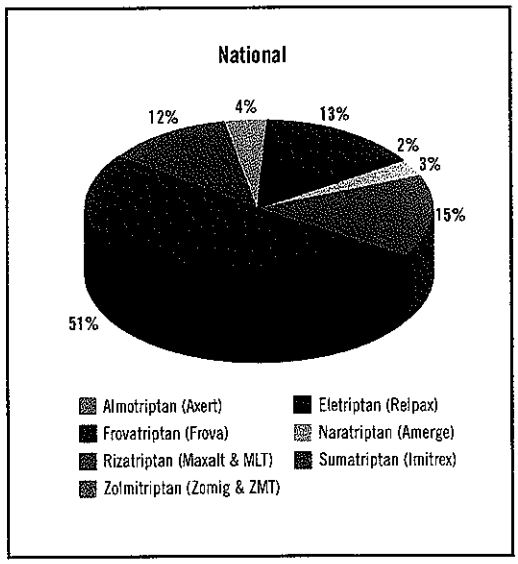


Figure 7. Triptan Prescriptions Dispensed at Retail Pharmacies Nationally
Source: IMS Health

Dihydroergotamine nasal spray (Migranal)[34] can deliver prompt relief for some patients, but its use can be associated with nausea. Ergotamine/caffeine combinations[35,36] may offer relief to some patients with moderate to severe migraine. The ergots also interact with serotonin receptors, but have a broader action on multiple receptor types (*eg*, dopamine). This broader action may be useful in patients who do not respond to triptans. Antiemetic agents such as trimethobenzamide (Tigan), promethazine (Phenergan) and prochlorperazine (Compazine), which is available in suppository form, can be useful for patients with severe nausea or vomiting.

Patients' degree of disability can help to direct selection of medication. The MIDAS Questionnaire,[37,38] which can be reproduced for use in your clinical practice, is a validated means of assessing migraine disability, to better individualize headache treatment. MIDAS is a widely accepted and useful marker for migraine disability, although somewhat limited by its reliance on retrospective patient information and accurate recall. Moreover, it does not take into account individual somatic threshold, such as that of a stoic individual who forces him- or herself to go to work despite the pain and other symptoms. Such an individual would have a low MIDAS score relative to the degree of pain. MIDAS scores can be useful in matching treatments to patients.

MIDAS QUESTIONNAIRE[36,37]

INSTRUCTIONS: Please answer the following questions about ALL your headaches you have had over the last 3 months. Write your answer in the box next to each question. Write zero if you did not do the activity in the last 3 months.

1	On how many days in the last 3 months did you miss work or school because of your headaches?	☐ days
2	How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school)	☐ days
3	On how many days in the last 3 months did you not do household work because of your headaches?	☐ days
4	How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? (Do not include days you counted in question 3 where you did not do household work)	☐ days
5	On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?	☐ days
	TOTAL	☐ days
A	On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day)	☐ days
B	On a scale of 0-10, on average, how painful were these headaches? (Where 0 = no pain at all, and 10 = pain as bad as it could be)	☐ days

Once you have filled in the questionnaire, add up the total number of days from questions 1-5 (Ignore A and B)

Your MIDAS Score....

Grade 1– Minimal or Infrequent Disability (score 0-5)

Grading System for the MIDAS Questionnaire:

Grade	Definition	Score
I	Minimal or infrequent disability	0-5
II	Mild or infrequent disability	6-10
III	Moderate disability	11-20
IV	Severe disability	21+

More...

Treatment Recommendations Based on Midas Score

Score	Grade	Definition	Recommendations
0-5	I	Little or no disabilty	• OTC analgesics may be effective • First-line treatment may benefit patients with infrequent but severe migraine • Patients who do not obtain effective relief with OTC analgesics may benefit from triptans
6-10	II	Mild disabilty	Acute prescription medicine may be necessary if • Headaches are severe • Headaches cause severe disruption in patients' lives • Patients have failed to obtain relief with OTC analgesics
21+	III	Moderate disabilty	• Specific therapy is usually most appropriate • Prophylactic treatment may be considered
	IV	Severe disability	Note: Very high MIDAS scores may indicate high frequency of nonmigraine headache; these patients should be managed accordingly

Although the MIDAS score is useful in suggesting treatment based on disability, the American Academy of Neurology (AAN) has developed practice parameters[24] on the general principles of migraine management.

AAN General principles of management[24]

- *Establish a diagnosis.*
- *Educate migraine sufferers about their condition and its treatment. Discuss the rationale for a particular treatment, how to use it, and what adverse events are likely.*
- *Establish realistic patient expectations by setting appropriate goals and discussing the expected benefits of therapy and how long it will take to achieve them. Empower the patients to be actively involved in their own management by encouraging patients to track their own progress through the use of diary cards, flow charts, headache calendars, and forms for tracking days of disability or missed work, school, or family activities. Treatment choice depends on the frequency and severity of attacks, the presence and degree of temporary disability, and associated symptoms such as nausea and vomiting.*
- *Create a formal management plan and individualize management: consider the patient's response to, and tolerance for, specific medications. Consider comorbidity/coexisting conditions. Coexisting conditions (such as heart disease, pregnancy, and uncontrolled hypertension) need to be ascertained as they may limit treatment choices.*
- *Encourage the patient to identify and avoid triggers.*

Acute treatment. Goals of acute migraine treatment are as follows:

1. *Treat attacks rapidly and consistently without recurrence.*
2. *Restore the patient's ability to function.*
3. *Minimize the use of back-up and rescue medications. (A rescue medication is used at home when other treatments fail and permits the patient to achieve relief without the discomfort and expense of a visit to the physician's office or emergency department.)*
4. *Optimize self-care and reduce subsequent use of resources.*
5. *Be cost-effective for overall management.*
6. *Have minimal or no adverse events.*

To meet these goals:

- *Use migraine-specific agents (triptans, dihydroergotamine [DHE]) in patients with moderate or severe migraine or whose mild-to-moderate headaches respond poorly to nonsteroidal anti-inflammatory drugs (NSAIDs) or combinations such as aspirin plus acetaminophen plus caffeine. Failure to use an effective treatment promptly may increase pain, disability, and the impact of the headache.*
- *Select a nonoral route of administration for patients with migraine associated with severe nausea or vomiting. Antiemetics should not be restricted to patients who are vomiting or likely to vomit. Nausea itself is one of the most aversive and disabling symptoms of a migraine attack and should be treated appropriately.*
- *Consider a self-administered rescue medication for patients with severe migraine who do not respond to (or fail) other treatments.*
- *Guard against medication-overuse headache ("rebound headache" or "drug-induced headache"). Frequent use of acute medications (ergotamine [not DHE], opiates, triptans, simple analgesics, and mixed analgesics containing butalbital, caffeine, or isometheptene) is generally thought to cause medication-overuse headache. Many experts limit acute therapy to two headache days per week on a regular basis. Patients with medication overuse should use preventive therapy.*

Prophylactic Therapy

The goals of migraine preventive treatment are to reduce attack frequency, severity, and duration; to improve responsiveness to treatment of acute attacks; and to improve function and reduce disability. Reasons to consider prophylactic therapy include[24]:

- Recurrent migraines that, in the patient's opinion, significantly interfere with daily life, despite use of acute treatment
- Frequent headaches
- Contraindication to or failure or overuse of acute therapies
- Adverse events with acute therapies
- Cost of both acute and preventive therapies
- Patient preference
- Presence of uncommon migraine conditions such as hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarction (to prevent neurologic damage—as based on expert consensus)
- Frequent use of acute treatment medications

Therapy should be instituted with medications with the highest levels of evidence-based efficacy at the lowest effective dose. Dosage can be increased gradually until clinical benefits are evident or until dosage is limited by adverse events. Improvement may not be evident for 2 to three months, so it is important to counsel patients about giving these agents an adequate trial. Efficacy should be monitored through the use of a headache diary and therapy can be re-evaluated after 3 to 6 months.[24] Agents commonly used in migraine prophylaxis are listed in Table 2.[24] Some clinicians prefer monthly follow-up, particularly in patients with frequent headache or who are at risk of overusing medication, until the headache pattern and dosage and tolerability of preventive medication has been stabilized. When prescribing prophylactic therapy, keep in mind that use of an opioid analgesic on a chronic basis can lead to intractable headache; patients with intractable headache should be referred to tertiary care headache centers or to headache specialists.

Table 2. Agents Used for Migraine Prophylaxis[24-26]

Generic (Brand)	Dose Range Mg/d	Weight of Evidence
Propranolol (Inderal)	60-480	A
Atenolol (tenormin)	25-100	B
Metoprolol (Lopressor)	100-400	B
Timolol (Blocadren)	20-30	A
Nadolol (Corgard)	40-240	B
Verapamil (Calan)	240-960	B
Amitriptyline (Elavil)	10-150	A
Fluoxetine (Prozac)	20-80	B
Topiramate (Topamax)	25-800	A*
Divalproex (Depakote)	500-1500	A
Gabapentin (Neurontin)	600-3600	B
Naproxen (Naprosyn)	375-1000	B
Magnesium	400-800	B
Riboflavin (Vitamin B2)	200-400	B
Feverfew	100-400	B

*Topiramate was approved for migraine prophylaxis after publication of AAN Guidelines.

Strength of evidence (quality of evidence)

Grade A. Multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings.

Grade B. Some evidence from randomized clinical trials supported the recommendation, but the scientific support was not optimal. For instance, few randomized trials existed, the trials that did exist were somewhat inconsistent, or the trials were not directly relevant to the recommendation. An example of the last point would be the case where trials were conducted using a study group that differed from the target group of the recommendation.

References

1. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia*. 2004;24 Suppl 1:9-160.
2. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. Jul-Aug 2001;41(7):646-657.
3. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. *JAMA*. Jan 1 1992;267(1):64-69.
4. Stewart WF, Lipton RB, Liberman J. Variation in migraine prevalence by race. *Neurology*. Jul 1996;47(1):52-59.
5. Tepper S, Martin V, Burch S, al e. Acute headache treatments in patients with health care coverage: What prescriptions are doctors writing? *Headache & Pain*. 2006;17:11-17.
6. Saper JR, Magee KR. Sinus Headache: Madison Avenue's gift to medicine. *Freedom from Headaches: a personal guide for understanding and treating headache*. New York: Simon and Schuster, Inc.; 1978.
7. Cady RK, Schreiber CP. Sinus headache: a clinical conundrum. *Otolaryngol Clin North Am*. Apr 2004;37(2):267-288.
8. Schreiber CP, Hutchinson S, Webster CJ, Ames M, Richardson MS, Powers C. Prevalence of migraine in patients with a history of self-reported or physician-diagnosed "sinus" headache. *Arch Intern Med*. Sep 13 2004;164(16):1769-1772.
9. Blau J. Adult migraine: the patient observed. In: Blau J, ed. *Migraine: Clinical and Research Aspects*. Baltimore: Johns Hopkins University Press; 1987:3-17.
10. Cady RK. Diagnosis and treatment of migraine. *Clin Cornerstone*. 1999;1(6):21-32.
11. Cady RK, Borchert LD, Spalding W, Hart CC, Sheftell FD. Simple and Efficient Recognition of Migraine With 3-Question Headache Screen. *Headache: The Journal of Head and Face Pain*. 2004;44(4):323-327.
12. Lipton RB, Dodick D, Sadovsky R, et al. A self-administered screener for migraine in primary care: The ID Migraine validation study. *Neurology*. Aug 12 2003;61(3):375-382.
13. Taylor F, Hutchinson S, Graff-Radford S, Cady R, Harris L. Diagnosis and management of migraine in family practice. *J Fam Pract*. Jan 2004; Suppl:S3-24.
14. Tepper SJ, Dahlof CGH, Dowson A, et al. Prevalence and Diagnosis of Migraine in Patients Consulting Their Physician With a Complaint of Headache: Data From the Landmark Study doi:10.1111/j.1526-4610.2004.04167.x. *Headache: The Journal of Head and Face Pain*. 2004;44(9):856-864.
15. Silberstein SD, Lipton RB, Goadsby PJ. *Headache in Clinical Practice*, 2nd ed. New York: Taylor & Francis; 2002.
16. Headache Classification Subcommittee of the International Headache Society. International Classification of Headache Disorders, 2nd ed. *Cephalalgia*. 2004;24 (Suppl 1):150.
17. Hamelsky SW, Lipton RB. Psychiatric comorbidity of migraine. *Headache*. Oct 2006;46(9):1327-1333.
18. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in women. *JAMA*. Jul 19 2006;296(3):283-291.
19. Nuyen J, Schellevis FG, Satariano WA, et al. Comorbidity was associated with neurologic and psychiatric diseases: A general practice-based controlled study. *J Clin Epidemiol*. Dec 2006;59(12):1274-1284.
20. Bigal ME, Rapoport AM, Sheftell FD, Tepper SJ, Lipton RB. Transformed migraine and medication overuse in a tertiary headache centre—clinical characteristics and treatment outcomes. *Cephalalgia*. Jun 2004;24(6):483-490.
21. Bigal ME, Sheftell FD, Rapoport AM, Tepper SJ, Lipton RB. Chronic daily headache: identification of factors associated with induction and transformation. *Headache*. Jul-Aug 2002;42(7):575-581.
22. Tepper SJ. Debate: analgesic overuse is a cause, not consequence, of chronic daily headache. Analgesic overuse is a cause of chronic daily headache. *Headache*. Jun 2002;42(6):543-547.
23. Smith TR, Sunshine A, Stark SR, Littlefield DE, Spruill SE, Alexander WJ. Sumatriptan and naproxen sodium for the acute treatment of migraine. *Headache*. Sep 2005;45(8):983-991.
24. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. Sep 26 2000;55(6):754-762.
25. Silberstein SD. Clinical practice guidelines. *Cephalalgia*. Oct 2005;25(10):765-766.
26. Silberstein SD, Rosenberg J. Multispecialty consensus on diagnosis and treatment of headache. *Neurology*. Apr 25 2000;54(8):1553.
27. Amerge [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2003.
28. Frova Complete Prescribing Information. Chadds Ford, Pennsylvania: Endo Pharmaceuticals; 2005 (2004).
29. Zomig [prescribing information]. Wilmington, DE: Astra-Zeneca Pharmaceuticals; 2003.
30. Imitrex [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2004.
31. Maxalt [prescribing information]. Whitehouse Station, NJ: Merck & Co, Inc, 2003.
32. Relpax [prescribing information]. New York, NY: Pfizer; 2003.
33. Axert [prescribing information]. Raritan, NJ: Ortho-McNeil Pharmaceutical Inc; 2003.
34. Migranal [prescribing information].
35. Wigraine [prescribing information].
36. Cafergot [prescribing information].
37. Lipton RB, Silberstein SD. The role of headache-related disability in migraine management: implications for headache treatment guidelines. *Neurology*. 2001;56(6 Suppl 1):S35-42.
38. Lipton RB, Stewart WF, Sawyer J, Edmeads JG. Clinical utility of an instrument assessing migraine disability: the Migraine Disability Assessment (MIDAS) questionnaire. *Headache*. Oct 2001;41(9):854-861.

Program Evaluation

1. The program provided useful information on the prevalence of migraine and related disability.
2. The program provided useful information on the screening and diagnosis of migraine headache.
3. The program provided me with adequate information on evidenced-based pharmacotherapeutics.
4. The format of this program met my educational needs.
5. Based on the information in the AMA *Therapeutics Insights* newsletter, what changes do you anticipate making in your approach to migraine management.

Evaluation Responses

	Strongly Agree	*Agree*	*Neutral*	*Disagree*	*Strongly Disagree*
Q.1	1	2	3	4	5
Q.2	1	2	3	4	5
Q.3	1	2	3	4	5
Q.4	1	2	3	4	5
Q.5					

DISCLOSURE POLICY
We believe that readers need to be aware of any affiliation or financial relationship (consultancies, honoraria, research grants, speakers' bureau, etc) between an author or members of the CME Advisory Board and any organization or entity that has a direct financial interest in the subject matter of the materials about which this CME program is written. We therefore obtain a complete disclosure and attestation form to inform the reader of any pertinent relationships disclosed, provided here. All content is peer reviewed, and the AMA has control over all final content.

Roger Cady:	Consultant: Aradigm Corp., GlaxoSmithKline, Jazz Pharmaceutical, Ortho-McNeil. Advisory Board: Allergan, Atrix Labs, Capnia, Endo, GlaxoSmithKline, Johnson & Johnson, Med Point, Merck & Co., Ortho-McNeil, Winston Labs. Research Grant: Abbott, AdvanceBionics, Alizyme, Allergan, Alexa, Aradigm, Capnia, Cipher, Eisai, Endo, GelStat, GlaxoSmithKline, Jazz Pharmaceutical, Johnson & Johnson, MAP Pharmaceutical, Matrixx, Merck & Co., Neuralieve, Novartis, Ortho-McNeil, Pfizer, Pozen, Torrey Pines, Vernalis
Richard Lipton:	Research grants, honoraria: Advanced Bionics, Allergan, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cierra, Endo, GlaxoSmithKline, Johnson & Johnson, Merck, Neuralieve, Ortho-McNeil, Pfizer, Pozen, ProEthics
Joel Saper:	Speaker's Bureau: GlaxoSmithKline, Merck, Elan, AstraZeneca, Pfizer, OMP Research Grant: GlaxoSmithKline, Merck, Abbott, AstraZeneca, OMP, Novartis, Johnson & Johnson, Allergan, Eisai, Advanced Bionics, Medtronic, Renovis, Pozen, ANS Consultant: GlaxoSmithKline, Elan, AstraZeneca, Pfizer, OMP, Allergan, Advanced Bionics, Medtronic, Pozen, Endo, ANS, PenWest
Stephen Silberstein:	Research Grant: Abbott, Advanced Bionics, AGA, Allergan, Advanced Neuro-Modulation System, AstraZeneca, Endo Pharmaceuticals, GlaxoSmithKline, Lilly, Medtronic, Merck, Ortho-McNeil, Pfizer, Pozen, Valeant Advisory Board: Allergan, Endo, GlaxoSmithKline, Medtronic, Merck, Ortho-McNeil, Pfizer, Pozen, Valeant Speakers' Bureau: AstraZeneca, GlaxoSmithKline, Merck, Ortho-McNeil
R. Mark Evans	Nothing relevant to disclose
Patti Fitzgerald	Nothing relevant to disclose
Adrienne Harkavy	Nothing relevant to disclose

Self-Assessment Questions

You may receive your CME certificate online by going to www.ama-assn.org/go/therapeuticinsights and completing the self-assessment and program evaluation. Alternatively, you use this answer sheet provided with the AMA Therapeutic Insights *newsletter. Please record your answers and either fax to 312-464-4849 or mail to: Healthcare Education Products*
Therapeutic Insights
American Medical Association
515 N. State Street
Chicago, IL 60610

(Please circle)

1. What percentage of migraine patients experience headache-associated functional impairment?
   a. 12%
   b. 24%
   c. 72%
   d. 91%
      1. a
      2. b
      3. c
      4. d
2. What percentage of patients diagnosed with migraine receive a prescription for migraine-specific pharmacotherapy?
   a. 50%
   b. 90%
   c. 37%
   d. 25%
      1. a
      2. b
      3. c
      4. d
3. Which patient prescreening questions are associated with a high positive predictive value for migraine headache?
   a. Are you nauseated or sick to your stomach when you have a headache?
   b. Do you have nasal congestion and rhinorrhea?
   c. Has a headache limited your activities for one or more days during the past 3 months?
   d. Does light bother you when you have a headache?
      1. All of the above
      2. a, b, and d
      3. a, c, and d
      4. a and d
4. In order to meet the goals of acute treatment of migraine, which of the following statements are TRUE?
   a. Recommend opioid analgesics for acute attacks
   b. Promptly use migraine-specific agents (triptans, dihydroergotamine) for moderate to severe migraine
   c. Guard against medication overuse headache or "rebound headache" that can occur with all medications for acute migraine
   d. Avoid antiemetic medications
      1. a, b and c
      2. b, c and d
      3. b and c
      4. a, b, and c