

Assessing the Chiral Switch: Approval and Use of Single-Enantiomer Drugs, 2001 to 2011

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Objectives: A “chiral switch” occurs in the pharmaceutical market when a drug made up of 2 enantiomer forms is replaced with a purified single-enantiomer version, often in the context of a patent expiration. We studied the prevalence of chiral switching in the United States over the past decade, including trends in use of, and expenditures on, these products in Medicaid.

Study Design: Retrospective analysis.

Methods: We used US Adopted Names prefixes (lev/levo/ar/es/dex/dextro) to identify all single-enantiomer drugs approved from 2001 to 2011. From publicly available US Food and Drug Administration (FDA) approval documents, we extracted the characteristics of the pivotal premarket trials for the single enantiomers. Specifically, we evaluated whether the single enantiomer was directly compared with the precursor racemic drug and whether there was evidence of superior efficacy. We used quarterly drug expenditure data from each state Medicaid program to chart trends in use of, and spending on, the single-enantiomer products and their racemic precursors during the study period.

Results: From 2001 to 2011, the FDA approved 9 single-enantiomer products: dexlansoprazole, levoleucovorin, levocetirizine, armodafinil, arformoterol, eszopiclone, escitalopram, dexamethylphenidate, and esomeprazole. Of those 9 drugs, 3 had at least 1 pre-approval randomized trial that included the racemic precursor as a direct comparator, but there was no evidence of superiority of the single enantiomer over the racemic at comparable doses. Between 2001 and 2011, US Medicaid programs spent approximately \$6.3 billion on these 9 single-enantiomer drugs.

Conclusions: Recently approved single-enantiomer drugs showed no evidence of superior efficacy over the older racemic precursors in the pivotal trials leading to their approval, and in a majority of cases, they were not directly compared.

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Most physicians, and certainly most patients, have never heard of the “chiral switch.”¹ A chiral drug is a single molecule product that exists in 2 mirror image forms, called enantiomers.² Despite their similar chemical structures, enantiomers can have different biological properties.³ For example, some enzymatic processes can distinguish between the R- (from the Latin *rectus* for “right”) and S- (from the Latin *sinister* for “left”) enantiomers,^{4,5} such that 1 enantiomer may be responsible for much of the pharmaceutical benefit while the other is inactive or even harmful.^{1,6-9} The phrase “chiral switch” was coined to refer to the substitution in the marketplace of a racemic drug (the name for a 50:50 mixture of 2 enantiomers) with a single-enantiomer version.

One prominent example of a chiral switch occurred in 2001, when the US Food and Drug Administration (FDA) approved AstraZeneca’s esomeprazole (Nexium), a proton pump inhibitor (PPI) used to treat gastroesophageal reflux disease and erosive esophagitis. At that point, the PPI marketplace was dominated by AstraZeneca’s omeprazole (Prilosec), which had been approved in 1989. Marketed as “the purple pill,” omeprazole earned over \$6 billion per year in the United States by 2000, although the key patents protecting its market exclusivity ended in 2001, opening the door to generic competition.¹⁰ Omeprazole is a racemic mixture of R-omeprazole and S-omeprazole, while esomeprazole, as its name implies, is isolated S-omeprazole. The S-omeprazole enantiomer was responsible for the drug’s clinical properties while the R-omeprazole enantiomer was inactive. After FDA approval, esomeprazole was marketed as “the new purple pill” to be used in place of generic omeprazole.

Chiral switching is a controversial practice. Some claim that single-enantiomer drugs offer little clinical advantage and are used by pharmaceutical manufacturers to perpetuate revenues as the original racemic pill approaches the end of its market exclusivity. The case of esomeprazole, in fact, has been cited as an example of “corporate waste” of healthcare resources.¹¹ However, in some cases, single enantiomers may offer benefit to patients, particularly if the inactive enantiomer may also be responsible for unwanted side effects; manufacturers may pursue single-enantiomer development because of this potential for improved safety or efficacy. Indeed,

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in guidance originally issued in 1992, and most recently updated in 2011, the FDA identified examples of drug toxicity associated with 1 member of a pair of enantiomers.¹²

Regardless of the motivation for development of a single-enantiomer drug, the FDA review and approval process is the same. New medications are generally approved by the FDA on the basis of effectiveness in reaching a particular outcome, and an improvement over placebo is commonly accepted.¹³ Since the FDA cannot by law require active comparators in clinical trials leading to drug approvals,^{14,15} single-enantiomer products can reach the market by demonstrating improvement over placebo, not their closely related racemic precursors.

How prevalent is chiral switching in the United States? To address that question, we identified all single-enantiomer medications approved from 2001 to 2011 with racemic mixtures already on the market. We examined FDA documents from the approval of these medications, focusing on their pivotal clinical trials and identifying whether the single-enantiomer version was formally compared with the racemic drug in the course of FDA approval. Finally, we use national data on prescription use and expenditures in Medicaid to illustrate the costs associated with their entry and trends in their use.

METHODS

Data Sources

We used the FDA database of drug approvals to identify all new single-enantiomer products approved for use between 2001 and 2011 that originated from an already FDA-approved racemic mixture. We systematically searched for all United States Adopted Names (USAN) prefixes assigned to drugs with a single-enantiomer formulation: lev-/levo- for the levorotatory, S-isomer form; ar- for the levorotatory, R-isomer form; es- for the dextrorotatory, S-isomer form; and dex-/dextro- for the dextrorotatory, R-isomer form.

Data Extraction

We extracted the manufacturer name and approval year for each identified drug. We then examined the FDA approval letter(s), summary review, and medical review(s) for each of the single-enantiomer drugs, along with the approved label, and collected reports of the pivotal trials leading to FDA approval. From these reports, we extracted whether the single enantiomer was compared with the racemic mixture in those trials and whether there was any evidence of superior efficacy. We also identified whether these comparisons to the racemic

Take-Away Points

From 2001 to 2011, the US Food and Drug Administration approved 9 single-enantiomer drugs with racemic precursors. Only 3 had pre-approval studies that compared the single-enantiomer with its precursor, and none showed evidence of improved patient outcomes.

- US Medicaid programs spent approximately \$6.3 billion on these 9 single-enantiomer drugs during this period.
- Well-designed comparative trials are needed to clarify, soon after approval, whether a single-enantiomer drug represents a measurable, cost-effective improvement over current racemic therapy.
- Large healthcare organizations that bear the brunt of these costs should use their position to educate prescribers about appropriate use of single-enantiomer products.

mixture were reported on the approved drug label. Since no pre-approval studies were powered to assess comparative safety, we focused on efficacy.

Medicaid Use and Expenditure

For a more detailed investigation of chiral switching, we focused on esomeprazole (Nexium) and escitalopram (Lexapro), the 2 single-isomer drugs identified in our search with the largest revenue in the past decade. These drugs were also approved early in our study period, giving us adequate time to examine trends in prescription use. Our data source was the Centers for Medicare & Medicaid Services (CMS), which provides aggregated quarterly drug expenditure data from each state Medicaid program categorized by National Drug Code (NDC).¹⁶ We used the NDC code to link the drugs and their racemic counterparts to the National Drug Data File (NDDF) (First Data Bank, National Drug Data File, San Bruno, CA: Hearst Corporation, 2012). For each drug, we identified the total number of prescriptions filled and the amount spent on the drug by state Medicaid programs in each calendar quarter. For 49 states and the District of Columbia (Arizona data were not available), we analyzed data from 1999 through the most recent quarter of Medicaid data available at the time of the analysis.

RESULTS

From 2001 through 2011, the FDA approved 9 single-enantiomer versions of racemic products (**Table 1**). Eight of the drugs had racemic precursors available in the United States. The lone exception was eszopiclone (Lunesta), whose precursor zopiclone (Imovane, Zimovane) was only commercially available outside the United States. Three of the 9 drugs—levoleucovorin (Fusilev), levocetirizine (Xyzal), and arformoterol (Brovana)—came from manufacturers other than the one that applied for approval of the racemic drug. The drugs covered a range of indications from depression to chronic obstructive pulmonary disease (COPD).

■ **Table 1.** Single-Enantiomer Drugs Approved in the United States From 2001 to 2011 and Their Racemic Precursors

Single-Enantiomer Drug (brand name)	Manufacturer	Year Approved	Approved Indication(s)	Racemic Precursor (brand name)	Manufacturer	Year Approved
Dexmethylphenidate (Focalin)	Novartis/Celgene	2001	Attention deficit/hyperactivity disorder	Methylphenidate (Ritalin)	Novartis	1955
Esomeprazole (Nexium)	AstraZeneca	2001	Gastroesophageal reflux disease and erosive esophagitis	Omeprazole (Prilosec)	AstraZeneca	1989
Escitalopram (Lexapro)	Forest	2002	Major depression and depression maintenance in adults	Citalopram (Celexa)	Forest	1998
Eszopiclone (Lunesta)	Sunovion/Sepracor	2004	Insomnia	Zopiclone (Imovane, Zimovane)	Rhone-Poulenc ^a	1986 ^a
Arformoterol (Brovana)	Sunovion/Sepracor	2006	Chronic obstructive pulmonary disease	Formoterol (Foradil)	Novartis	2001
Armodafinil (Nuvigil)	Cephalon	2007	Narcolepsy and shift-work sleep disorder	Modafinil (Provigil)	Cephalon	1998
Levocetirizine (Xyzal)	Sanofi-Aventis	2007	Seasonal allergic rhinitis, perennial allergic rhinitis, chronic idiopathic urticaria	Cetirizine (Zyrtec)	Pfizer	1995
Levoleucovorin (Fusilev)	Spectrum	2008	Rescue after high-dose methotrexate therapy in osteosarcoma	Leucovorin	Glaxo	1952
Dexlansoprazole (Dexilant)	Takeda	2009	Gastroesophageal reflux disease and erosive esophagitis	Lansoprazole (Prevacid)	TAD/Takeda	1995

^aZopiclone is not commercially available in the United States. These data reflect its introduction in Europe.

Comparative Efficacy of Single-Enantiomer and Racemic Drugs

Three of the 9 single-enantiomer drugs had at least 1 pre-approval randomized, controlled trial that included the racemic precursor as a direct comparator (Table 2). Esomeprazole 40 mg demonstrated statistically significant efficacy over omeprazole 20 mg in 2 studies, although it was not superior in 2 other studies. However, pharmacologically equivalent doses of the racemic and enantiomer medications were not compared in these studies, as 40 mg of the single-enantiomer product would contain at least 3 times as much of the active S-isomer as 20 mg of racemic omeprazole on a per milligram basis.¹⁷ Dexlansoprazole (Dexilant) and levocetirizine (Xyzal) demonstrated efficacy similar to that of their racemic predecessors in the pre-approval studies. Two additional drugs—escitalopram (Lexapro) and dexmethylphenidate (Focalin)—included the racemic as an active control in pre-approval studies but compared the 2 arms with placebo, not with each other.

Trends in the Use of Esomeprazole and Escitalopram

Between 2001 and 2011, Medicaid programs nationally spent approximately \$6.3 billion on the 9 single-enantiomer drugs we reviewed (Table 3). The 2 greatest contributors to

this total were esomeprazole (\$3.5 billion) and escitalopram (\$1.8 billion), each representing over 60% of total Medicaid spending on the single-enantiomer and racemic precursor over that time period. Dexmethylphenidate spending was \$678 million from 2001 to 2011, while the single enantiomers approved after 2004 generated substantially lower Medicaid spending

After esomeprazole's approval in 2001, its use in Medicaid quickly surpassed omeprazole's and peaked at over 1 million prescriptions per quarter in the second half of 2005 (Figure 1). Generic omeprazole entered the market in the fourth quarter of 2002, became available as an over-the-counter drug in June 2003, and peaked in the third quarter of that year with almost 400,000 prescriptions. However, generic omeprazole did not surpass esomeprazole in number of prescriptions until early 2010. The data show an increase in the use of omeprazole between 2009 and 2011, potentially signifying enhanced coverage of over-the-counter omeprazole in Medicaid programs, which had largely excluded this version of the product in the mid-2000s.¹⁸ Esomeprazole represented almost one-third (32.7%) of prescriptions even at the end of the study period in the third quarter of 2011.

Escitalopram followed a similar pattern. After the introduction of escitalopram in 2002, its use in Medicaid rapidly

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■ **Table 2.** Studies Considered During FDA Approval for Selected Single-Enantiomer Drugs Approved, 2001 to 2011

Drug	Pre-approval RCTs (N)	Pre-approval RCTs With Active Racemic Controls (N)	Details of Active-Control Comparisons	Conclusion: Superior to Racemic?
Dexmethylphenidate	2	1 ^a	Efficacy in ADHD tested in one 4-week RCT with placebo and methylphenidate arms, but no comparison with active control (both better than placebo).	Not tested
Esomeprazole	8	4	Healing of erosive esophagitis tested in four 8-week RCTs with omeprazole as control. Esomeprazole (40 mg) found statistically superior to omeprazole (20 mg) in 2 trials. Esomeprazole (20 mg and 40 mg) found not statistically superior to omeprazole (20 mg) in 2 studies.	Mixed evidence at non-comparable doses
Escitalopram	2	2 ^a	Effect on major depressive disorder tested in two 8-week double-blind RCTs of escitalopram (10 mg and 20 mg), citalopram (20 mg and 40 mg), and placebo. Escitalopram found superior to placebo in 1 trial, but not directly compared with citalopram in either.	Not tested
Eszopiclone	6	0	N/A [racemic version not approved in US]	Not tested
Arformoterol	5	0	Efficacy in COPD tested in two 12-week RCTs, 1 open-label 1-year safety study, and 1 dose-ranging study with placebo and active control arms (salmeterol). No direct statistical comparison with active comparator.	Not tested
Armodafanil	4	0	N/A	Not tested
Levocetirizine	14	3	Effect on allergic rhinitis tested in one 1-week long RCT comparing levocetirizine (5 mg) with cetirizine (10 mg) and found non-inferior. Two RCTs testing onset of action included placebo and active control (cetirizine) arms, but there was no direct statistical comparison with active controls.	No
Levoleucovorin	0	0	Drug originally approved in 1991 based on response in 16 patients compared with 28 historical controls using racemic leucovorin. After removal from market due to manufacturing deficiencies, reapproved in 2007 with no new studies.	No
Dexlansoprazole	6	2	Healing of erosive esophagitis tested in two 8-week active control RCTs comparing dexlansoprazole (60 mg or 90 mg) with lansoprazole (30 mg). Dexlansoprazole found noninferior to lansoprazole. Dexlansoprazole 60 mg found superior to lansoprazole 30 mg in 1 trial, but not the other.	No

ADHD indicates attention deficit/hyperactivity disorder; COPD, chronic obstructive pulmonary disease; FDA, US Food and Drug Administration; RCT, randomized controlled trial.

^aIn the pre-approval RCTs for dexmethylphenidate and escitalopram, there was no direct comparison with the racemic precursor despite the presence of active control arms.

increased, such that by the second quarter of 2004, over 1 million prescriptions were filled per quarter (Figure 2). Generic citalopram entered the market in the fourth quarter of 2004, leading to a steep reduction in the use of brand name citalopram, and also a leveling off in the use of escitalopram, although the number of prescriptions for escitalopram continued to outnumber those for generic citalopram until the end of 2009. Prescriptions of all products fell in 2006

due to transition of dual-eligible elderly patients to Medicare Part D.

DISCUSSION

From 2001 to 2011, the FDA approved 9 single-enantiomer drugs, several of which reached blockbuster status in the United States.^{19,20} Despite substantial spending on enantio-

■ **Table 3.** Total National Medicaid Spending on Single Enantiomers and Their Racemic Precursors, 2001 to 2011

Drug (Approval Year)	Total Medicaid Spending on Single Enantiomer, 2001-2011 (\$, millions)	Total Medicaid Spending on Single Enantiomer and Racemic Precursor Combined, 2001-2011 (\$, millions) ^a	Percentage of Total Enantiomer and Racemic Reimbursement for the Enantiomer (%)
Dexmethylphenidate (2001)	\$678	\$1233	55%
Esomeprazole (2001)	3454	5640	61
Escitalopram (2002)	1813	2870	63
Eszopiclone (2004)	198	n/a ^b	—
Arformoterol (2006)	12	70	17
Armodafinil (2007)	11	366	3
Levocetirizine (2007)	28	1043	3
Levoleucovorin (2008)	3	33	9
Dexlansoprazole (2009)	68	5898	1

Source: Centers for Medicare & Medicaid Services.

^aMedicaid data are for 49 states and the District of Columbia; Arizona data were not available.

^bZopiclone, the racemic precursor of eszopiclone, is not commercially available in the United States.

mers, most of these drugs were not directly compared with their racemic precursor in the course of FDA approval, and when they were, there was no clear evidence of any improvements in patient outcomes.

In the postapproval period, there has also been little evidence showing any substantial comparative efficacy benefits of these single enantiomers over their racemic precursors. For example, a Cochrane systematic review of escitalopram's effectiveness identified 6 studies of varying methodological quality (both published and unpublished) directly comparing escitalopram with citalopram. Of the 6 studies, 3 showed a statistically significant advantage of escitalopram in the primary outcome of response to treatment, and each was industry funded.²¹ The review authors concluded that there was a potential for "overestimation of treatment effect due to sponsorship bias." The review also found in pooled analyses that escitalopram was no more effective than 3 other antidepressants in the same class (fluoxetine, paroxetine, and sertraline). Evidence of superior effectiveness did not emerge after esomeprazole's approval, either. The studies reviewed by the Drug Effectiveness Review Project found that comparisons between the enantiomer and racemic precursor uniformly compared esomeprazole at a pharmacologically superior dose (40 mg) with omeprazole (usually at a dose of 20 mg), limiting the possibility of making any conclusions about efficacy.²² The Cochrane review of treatment of gastroesophageal reflux concluded that different PPIs do not show statistically significant differences in effect at comparable dosages.²³ Notably, the 2 studies that showed superiority of esomeprazole over omeprazole in the pre-approval RCTs were published within 1 year of approval,^{24,25} while the 2 studies that showed no superiority were not published until 5 years later,^{26,27} again raising the

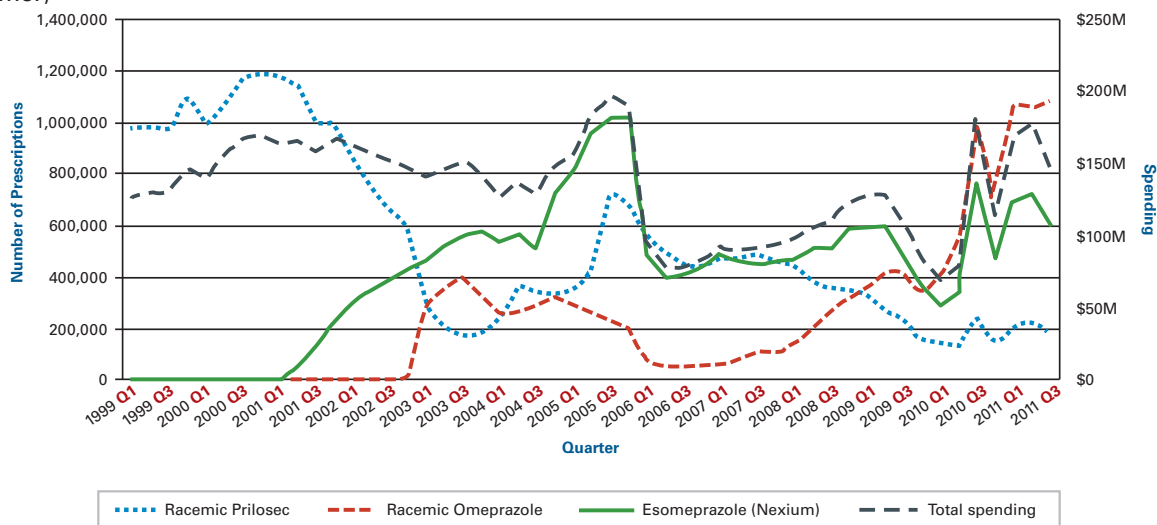
concern about publication bias for the postapproval comparative effectiveness studies.

Although there is no requirement for comparison of single-enantiomer drugs with their racemic precursors for FDA approval, we found numerous examples in the FDA reviews of experience with the racemic product being invoked to justify the need (or lack of need) for additional testing or guidance prior to approving the drugs. For example, while the FDA does not convene external advisory committee meetings for every drug application, it elected to not do so for dexlansoprazole specifically because the "product is not a new molecular entity. It is the R-enantiomer of a product that was approved in 1995."²⁸ In another instance, the Division of Pulmonary and Allergy Products did not request audits by the Division of Scientific Investigation because arformoterol "is the active enantiomer of the well-characterized LABA [long-acting beta-agonist], racemic formoterol, which is already approved for treatment of both asthma and COPD, the efficacy data are robust and as would be expected for the product, and the sponsor is not making any novel claims for the product."²⁹ Regulatory consideration of the safety of single-enantiomer products also benefitted from prior experience with racemic precursors. In the medical review for esomeprazole, the reviewer wrote, "Because Nexium is the S-enantiomer of omeprazole and omeprazole is a PPI that is perceived as safe, Nexium is also considered safe. Omeprazole has been marketed worldwide since 1988 and is presently available in 106 countries for various acid-related gastrointestinal disorders."¹⁷

Although we did not focus on comparative safety or tolerability of the enantiomers, it is conceivable that the benefit of single enantiomers is not in superior efficacy, but superior

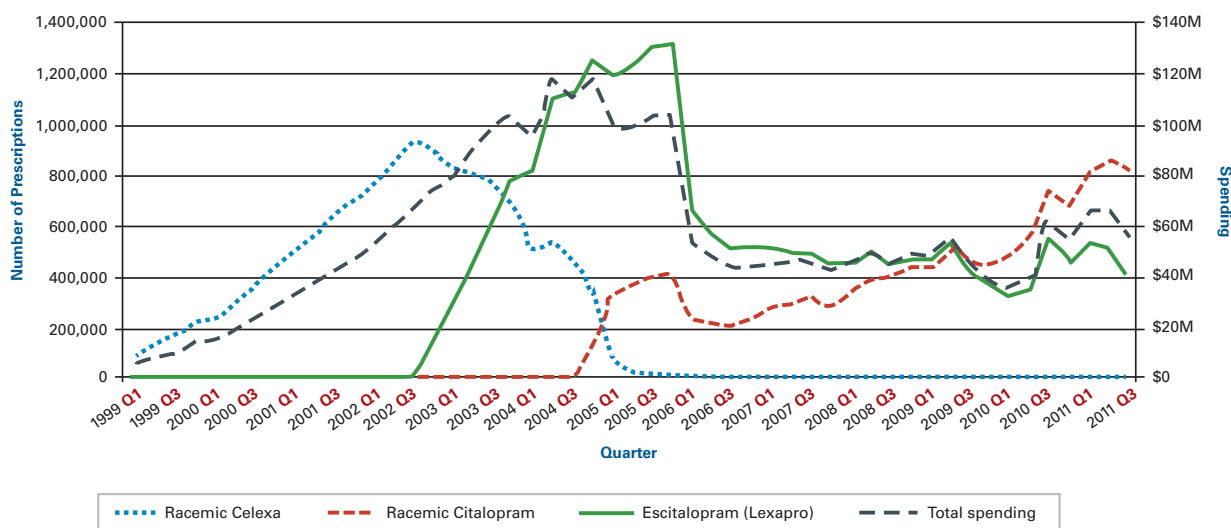
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Figure 1. Quarterly Prescriptions (left axis) and Total Spending (right axis) in State Medicaid Programs for Brand Name Prilosec (Racemic), Generic Omeprazole (Racemic), and Brand Name Esomeprazole (Nexium, Single Enantiomer)



Esomeprazole was FDA-approved in 2001 and is represented by the solid green line. Total quarterly spending by Medicaid for all 3 products is represented by the long-dashed line. Prescriptions of all products fell in 2006 due to transition of dual eligible elderly patients to Medicare Part D.

Figure 2. Quarterly Prescriptions (left axis) and Total Spending (right axis) in State Medicaid Programs for Brand Name Celexa (Racemic), Generic Citalopram (Racemic), and Brand Name Escitalopram (Lexapro, Single Enantiomer)



Escitalopram was FDA approved in 2002 and is represented by the solid green line. Total quarterly spending by Medicaid for all 3 products is represented by the long-dashed line. Prescriptions of all products fell in 2006 due to transition of dual eligible elderly patients to Medicare Part D.

tolerability or safety. We are not aware, however, of any strong evidence to support that hypothesis for the drugs we studied. For example, in the Cochrane review comparing escitalopram and citalopram, there was no difference between the 2 drugs in study discontinuation due to side effects or number of patients experiencing a side effect.²¹ Similarly, prior reviews have found no evidence of any difference in adverse events

(AEs) or withdrawals due to AEs across trials of PPIs.²² To be sure, there are past examples of chiral switching bringing about important safety benefits, as in the case of levodopa, a key treatment for Parkinson's disease; initially, the racemic drug caused significant AEs, but shifting to the single enantiomer reduced the AEs and allowed for a higher dose of the active drug.^{30,31}

Despite unclear efficacy or safety benefits, approval of enantiomer drugs over the past decade has had substantial cost implications. In the cases of esomeprazole and escitalopram, the enantiomer rapidly absorbed market share from the racemic precursor and diverted use of generic versions of the racemic product. Increasing the cost of medications with no discernible difference in health outcomes negatively impacts the health of patients taking those drugs. Higher prescription drug costs are associated with lower adherence, higher incidence of serious AEs, greater utilization of healthcare services, and worse health outcomes³²⁻³⁴ These costs must be weighed against any theoretical, or even real, improvement in patient outcomes with use of single-enantiomer formulations.

The case of armodafinil gives further insight into the use of enantiomers to maintain market share in products losing patent protection. Cephalon received approval for modafinil (Provigil) by the FDA in 1998. In 2002, 4 companies filed applications with the FDA for generic modafinil.³⁵ In order to maintain its market exclusivity, in 2006, Cephalon settled with those generic manufacturers for more than \$200 million, delaying entry of a generic modafinil until 2012. In 2007, Cephalon's single-enantiomer armodafinil (Nuvigil) was approved, meaning that the company then had 5 years to "switch" market share away from modafinil.³⁶ In order to encourage transition of modafinil to armodafinil, Cephalon steadily increased the price of modafinil, from \$6.80 per pill in 2008 to \$13.62 in 2009, by which time armodafinil was launched at \$8.98 per pill.³⁷ By 2011, sales of Nuvigil represented 42% of combined armodafinil/modafinil prescriptions in the United States.³⁸

Most patients are probably not aware that the single-enantiomer drugs they are prescribed are so closely related to precursor racemic mixtures. Linguistic similarities between generic names of racemic and enantiomer drugs will likely be missed by most physicians and patients, particularly since most drugs are referred to by their brand name, even after they are being produced by generic manufacturers.³⁹ Thus, naming conventions artificially inflate the differences between the single-enantiomer and racemic drugs.⁴⁰ If patients (and their physicians) were better educated about the clinical similarities between racemic and enantiomer drugs and were given greater insight into the trials that led to the approval of enantiomers, they may be less likely to pay higher prices for the medication.⁴¹⁻⁴³

A number of measures can be taken to facilitate more rational use of enantiomer drugs by physicians and patients. Although the FDA cannot require comparative efficacy testing prior to approval, the FDA should ensure that single-enantiomer drug labels highlight differences, or the lack of differences, in efficacy and safety from the racemic version.⁴⁴ Three enantiomer drugs in our sample had direct racemic comparators in approval trials, but only 2 of the labels mentioned the study results (dex-

lansoprazole and esomeprazole). Special attention should be paid to the single enantiomers when formulary tiering decisions are made by health plans, although heightened attention by insurers to the "chiral switch" may explain, in part, why spending on enantiomers, at least in Medicaid, appears to have slowed for single-enantiomer drugs approved in recent years (Table 3). For another solution, policy makers might look to India, where intellectual property laws prevent patents from regularly being issued on secondary formulations of previously discovered pharmaceutical products that lack substantial clinical benefits.⁴⁵ In the United States, such a change would require an amendment to the patent law, which does not distinguish between pharmaceutical formulations and other products.

Rapid uptake after approval of single-enantiomer drugs by patients and physicians represents a high financial burden on both the US healthcare system and individuals, without an obvious concomitant gain in patient health. More well-designed and widely disseminated comparative trials are needed to clarify, soon after approval, whether a new single enantiomer drug represents a measurable, cost-effective improvement over current racemic therapy. Large healthcare organizations that bear the brunt of these costs should use their position to educate prescribers about appropriate use of single-enantiomer and racemic products to slow the adoption of drugs with no real advantage over cheaper alternatives.

Study Limitations

This analysis of single-enantiomer drugs approved since 2001 used publicly available FDA reports, some of which included redacted text. However, such redactions are usually not related to approved-drug indications, so the likelihood that we missed important approval information is not great. We only examined labels at the time of approval, and so did not formally address comparisons between single-enantiomer drugs and their racemic counterparts that may have occurred after approval. Finally, we acknowledge that the FDA does not have legal authority to require comparative efficacy studies for drugs prior to approval and we do not conclude that the FDA erred in approving any of these drugs; there could, in fact, be efficacy or tolerability benefit for individual patients from single-enantiomer drugs that cannot be discerned from population-based randomized trial.⁴⁶ Nonetheless, our goal was to identify the prevalence of chiral switches and examine whether any comparative effectiveness studies were submitted as part of the approval process.

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