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Examining Product Risk in Context

Market Withdrawal of Zomepirac as a Case Study

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Objective.—To examine changes in the prescribing of analgesics after the market entry and subsequent withdrawal of zomepirac sodium, a nonsteroidal anti-inflammatory drug (NSAID), following repeated reports of zomepirac-related deaths.

Design.—To evaluate this natural quasi experiment, we conducted time-series analyses to compare prescribing in two cohorts of primary care physicians from July 1980 through September 1983.

Setting.—Study physicians provided outpatient pharmaceutical care to patients enrolled in the New Jersey Medicaid program.

Participants.—We identified 260 primary care physicians who provided 10 or more prescriptions for zomepirac (zomepirac prescribers) and 308 who provided 10 or more prescriptions for NSAIDs other than zomepirac (other-NSAID prescribers) in Medicaid during the study period.

Main Outcome Measures.—Monthly rates of prescribing for zomepirac and several categories of substitute analgesics among Medicaid patients seen by study physicians.

Main Results.—Zomepirac accounted for a stable 11.0% of analgesic prescribing among the zomepirac-prescriber cohort; label changes and manufacturer product-risk warnings 11 months before the product's withdrawal from the market had no impact on use. After market entry, zomepirac prescribers reduced use of other NSAIDs and propoxyphene (hydrochloride or napsylate) in comparison with other-NSAID prescribers (−8.1% and −2.8% of total analgesic prescribing, respectively; $P < .001$). After the product's withdrawal from the market, zomepirac prescribers showed significant increases in relative prescribing of other NSAIDs (+6.8%; $P < .001$), propoxyphene (+2.1%; $P < .05$), and analgesics containing barbiturates (+2.7%; $P < .001$).

Conclusions.—The sudden withdrawal of zomepirac from the market resulted in substitutions not only of other NSAIDs, but also of alternative analgesics that carry risks of habituation and adverse effects. Apparent gains in patient safety resulting from market withdrawal of medications must be evaluated in comparison with risks of medications likely to be substituted.

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DURING the past two decades, an increasing number of government, medical, and lay press reports have focused on the problem of unanticipated adverse reactions to prescription drugs.¹ Government and industry responses have ranged from modest label warnings² to withdrawal of the offending product from

the market, as in the recent case of triazolam in the United Kingdom.³ One rationale for product removal is an unstated assumption by regulators and policymakers that all clinical risks attributable to a drug are eliminated when it is withdrawn; rarely do they examine the comparative risks and benefits of alternative medications that may be substituted for the withdrawn product.⁴ We are not aware of any controlled studies that have examined this question. This investigation analyzes changes in the use of various alternative analgesics following the market entry and withdrawal of zomepirac sodium.

Zomepirac is a prostaglandin synthetase inhibitor, one of a class of analgesic products referred to collectively

as nonsteroidal anti-inflammatory drugs (NSAIDs). The drug was first marketed in the United States by McNeil Pharmaceutical, Spring House, Pa, in November 1980, under the proprietary name Zomax.⁵ Indications for which it was marketed included relief of moderate to severe postoperative pain, as well as acute and chronic orthopedic conditions, osteoarthritis, muscle-contraction headache, dysmenorrhea, and the chronic pain of cancer.⁶ Zomepirac achieved rapid acceptance, accounting for 11% of new analgesic prescriptions within 4 months of its introduction.^{7,8}

For editorial comment see p 1976.

The first report of an apparent anaphylactic reaction to zomepirac was published in April 1981, about 5 months after the product was released.⁹ In July 1981, McNeil included a mild warning in all product labeling stating that "reactions have been reported."¹⁰ After further case reports of zomepirac-associated anaphylaxis appeared in the medical literature,^{11,12} the manufacturer sent warning letters in April 1982 to 200 000 physicians, alerting them to the drug's potential for serious allergic reactions. However, 1 week later, the company launched a major 10-week sales campaign ("Operation 111") intended to increase sales of zomepirac and tolmetin, two of its most successful analgesics. On March 3, 1983, a Syracuse, NY, television report cited five zomepirac-associated deaths, including a dramatic account by a physician who suffered a life-threatening anaphylactic reaction.¹³ The following day, McNeil voluntarily recalled the product from the market.¹⁴ Following 2 years of lawsuits and hearings by both the Food and Drug Administration and Congress, McNeil permanently withdrew zomepirac in May 1985.¹⁵

Zomepirac's rapid capture of a sizable share of the analgesic market, followed by stable use for an extended period before sudden withdrawal, provides an opportunity to assess both expected and unanticipated substitution effects caused by market availability of a popular drug.

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Table 1.—Prescriptions for Study Analgesics per 100 Medicaid Recipients in Practice by Provider Specialty, July 1980 Through November 1981

Physician Group	Physicians, No.	Study Analgesics				All Study Analgesics
		Zomepirac Sodium	Other NSAIDs*	Analgesic With Opioids†	Analgesic With Barbiturates	
General practice	477	5.1	39.2	34.4	8.8	87.5
Internal medicine	468	5.5	73.7	55.3	12.9	147.4
Family practice	238	3.7	45.3	33.0	8.2	90.2
All Primary Care Physicians	1183	4.9	49.0	37.1	9.7	100.7
Dentistry, oral surgery	140	3.3	4.9	81.8	4.2	94.2
Pediatrics	121	0.2	2.7	4.9	0.7	8.5
General surgery	122	3.1	36.1	33.3	8.4	80.9
Obstetrics, gynecology	106	1.3	9.8	21.7	5.7	38.5
Other specialty	287	3.1	29.8	42.8	7.0	82.7
All Non-Primary Care Physicians	776	1.5	13.1	24.5	4.0	43.1

*NSAID indicates nonsteroidal anti-inflammatory drug.

†Analgesic products containing propoxyphene (hydrochloride or napsylate), pentazocine, meperidine hydrochloride, or codeine.

Few studies have examined drug substitution in a critical way,¹⁶ and even fewer have studied the comparative risks associated with substituted agents.¹⁷ Herein we analyze shifts in analgesic prescribing patterns associated with zomepirac's market entry; changes in product use during its market life span, particularly at the time of warnings about its safety; and the impact of its rapid withdrawal. We conclude with a discussion of the need to evaluate drugs in relation to their likely substitutes and implications for health policy decision making.

METHODS

Study Analgesics

We identified all drugs that were potential analgesic alternatives to zomepirac at the time of the study, as determined by an expert panel of physicians and clinical pharmacists familiar with research on Medicaid pharmaceutical practices. To be included in the study, a medication had to be marketed for the treatment of mild to moderate pain and be available by prescription only. The panel used contemporary drug compendia^{18,19} as references to aid in selecting alternative product classes and identifying all marketed products chemically equivalent to the generic entities contained in each class. The identified drugs were grouped into five categories: (1) zomepirac; (2) other NSAIDs; (3) analgesics containing propoxyphene (hydrochloride or napsylate); (4) analgesics containing another opioid (codeine, hydromorphone hydrochloride, meperidine hydrochloride, morphine sulfate, oxycodone, or pentazocine); and (5) analgesics containing barbiturates (combinations with butalbital). The "other-NSAID" category included all NSAIDs other than zomepirac that were available prior to 1984: benoxaprofen, diflunisal, fenoprofen, ibuprofen, indomethacin, meclizolam sodium, mefenamic acid, naproxen, oxyphenbutazone, phenylbutazone, piroxicam, sulin-

dac, and tolmetin. We did not include over-the-counter products such as acetaminophen or salicylates since we lacked complete data on their use.

The study drugs selected by the expert panel vary greatly in safety and efficacy. For example, zomepirac has been estimated to have 500 to 1000 times the risk of producing a severe anaphylactic reaction as other NSAIDs.¹⁵ The opioid analgesics can be habituating, and have also been associated with the occurrence of other adverse effects, including hip fracture.²⁰ Propoxyphene may be no more effective an analgesic than aspirin, and its use has been associated with a substantial number of overdose deaths.²¹ Other opioid analgesics such as meperidine can pose a risk of neuropsychiatric toxic effects.^{22,23} Finally, analgesics that contain long-acting barbiturates carry potential safety risks in dosing and liability for abuse.²⁴

Data Sources

Drug claims data from the New Jersey Medicaid Management Information System provided information on prescriptions filled and reimbursed during the 39-month study period (July 1980 through September 1983). All claims for the study analgesics were extracted from a previously selected 40% random sample of patients in the New Jersey Medicaid program who received at least one prescription for any drug during this period, a total of 173 726 individuals. The drug claims data used included recipient identifier, drug product code, date the prescription was filled, and a prescriber identification number.

We used these drug claims data to identify all physicians who prescribed one or more analgesic prescriptions to a member of this sample of New Jersey Medicaid drug recipients. Thus, physicians were not chosen randomly, but were selected by virtue of their prescribing to a random sample of drug

recipients. We also obtained a complete Medicaid provider file, which included the stated specialties of all physicians participating in the New Jersey Medicaid program during the study period. Using prescriber and recipient identifying numbers, we calculated for every provider the total number of unduplicated Medicaid recipients in our patient sample for whom a medication of any type was prescribed, which was used as a proxy for Medicaid practice size.

Selection of Physician Study Group

To describe changes in prescribing analgesics in a stable population of primary care providers, we first identified 1964 physicians, dentists, and osteopaths with at least one filled prescription for any study analgesic in every 6-month period throughout the study. This group, which was responsible for the majority of all analgesic prescriptions to our sample of New Jersey Medicaid recipients, averaged over 7600 analgesic prescriptions per month, or 4.4 analgesic prescriptions per 100 patients. Controlling for changes in prescribing due to the entry and withdrawal of zomepirac from the market, analgesic prescribing remained approximately constant during the follow-up period.

Since we were primarily interested in the prescribing of zomepirac in general ambulatory practice, we used the medical specialty data to identify 1183 primary care physicians, defined as general practitioners, family practitioners, and internists. These physicians represented 60% of consistent prescribers, and wrote a total of 475 600 reimbursed analgesic prescriptions (80.2% of the total) to 96 989 Medicaid patients (55.8% of total recipients of any drug) during the 39-month study. As indicated in Table 1, these primary care physicians were more likely than other providers to prescribe NSAIDs in general (53.9 prescriptions per 100 patients during

this period vs 14.6 prescriptions per 100 patients from other physicians) and zomepirac in particular (4.9 vs 1.5 prescriptions per 100 patients, respectively).

To examine product substitution effects in primary care, we identified 260 physicians who provided 10 or more zomepirac prescriptions during the 28-month period of product life from November 1980 through February 1983 (called zomepirac prescribers). Because other secular trends in drug utilization could conceivably have resulted in increased prescribing of some substitute drugs independent of the withdrawal of zomepirac, we constructed a comparison group of 308 primary care physicians who did not prescribe zomepirac, but who provided 10 or more prescriptions for other NSAIDs during the study period (called other-NSAID prescribers).

Data Analyses

We first constructed time series of analgesic utilization by computing the monthly number of analgesic prescriptions overall and within each analgesic category. All months were adjusted to contain the equivalent of 30 days. We then divided monthly utilization by the number of unduplicated Medicaid drug recipients in the practices of physicians in each group (as described above), expressing the results as utilization per 100 recipients. The resulting time-series data for total analgesic use were analyzed by specifying a segmented linear regression model with correction for serially autocorrelated observations.²⁵⁻²⁹ This model estimated the overall level and trend in analgesic prescribing during the study period, as well as the size and significance of any changes in level of prescribing (discontinuities) after zomepirac entered the market, and immediately following its withdrawal from the market. In this and in all other time-series models, data from November through December 1980 and March through April 1981, the periods of immediate market adjustment following zomepirac's release and withdrawal, respectively, were excluded to obtain more precise estimates.

For zomepirac, the time-series model applied only to the 28-month period it was on the market. We added a term to the model to estimate changes in zomepirac prescribing following the April 1982 nationwide warnings to physicians concerning adverse drug reactions.

Substitution effects were estimated by contrasting the time series for zomepirac prescribers vs other-NSAID prescribers in each of the five analgesic categories. We converted each drug category's monthly utilization data in each category to its proportion of total analgesic prescriptions (ie, the proportional

preference or market share of each category). This method provided both a stable measure of physician choice of analgesic, the behavior of interest, and controlled for any difference in rates of baseline analgesic prescribing between the two study groups. The resulting monthly time-series data were analyzed using segmented linear regression models. These models estimated, for the two prescriber cohorts, the underlying level and trend in proportional use of each analgesic category, and any discontinuities in use when zomepirac entered the market and when it was withdrawn. The same model also included terms to estimate any differences between zomepirac prescribers and other-NSAID prescribers in changes in analgesic preference when zomepirac entered the market and when it was withdrawn.²⁹

RESULTS

Zomepirac prescribers averaged 6.2 analgesic prescriptions per 100 recipients per month (95% confidence interval [CI], 5.9 to 6.6), compared with a slightly lower 5.5 analgesic prescriptions per 100 recipients (95% CI, 5.2 to 5.7) among other-NSAID prescribers. There was no observable trend in total analgesic use in either group during the study period. However, during the period zomepirac was on the market, total analgesic use rose among zomepirac prescribers by an estimated 0.5 prescriptions per month, although this rise was not significant (95% CI, -0.0 to 1.0).

The rapid acceptance and stability of zomepirac prescribing over time among the study cohort of zomepirac prescribers paralleled the patterns observed in the entire population of Medicaid physicians prescribing analgesics. After a rapid rise in prescribing during the first 2 months of its availability, zomepirac accounted for 11.0% of total analgesics prescribed in this group (95% CI, 10.4% to 11.6%; Fig 1, bottom). There was no discernible reduction in zomepirac prescribing by these primary care physicians associated with the April 1982 warning letter issued by McNeil concerning the potential for severe allergic reactions.

Other NSAIDs accounted for slightly less than half of all analgesic prescriptions in both primary care prescriber cohorts before zomepirac was released (Fig 1, top). The use of other NSAIDs rose significantly in both cohorts throughout the study period. However, once zomepirac became available, the trends in use diverged, with the rate of prescribing other NSAIDs increasing more slowly among zomepirac prescribers than among other-NSAID prescribers. After zomepirac was withdrawn

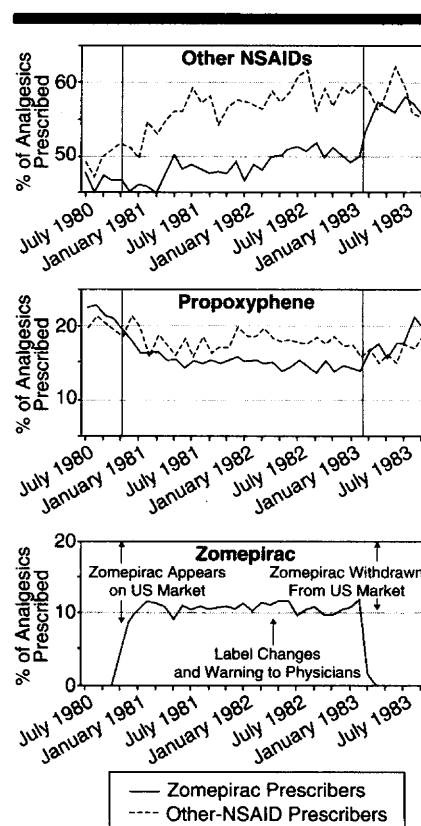


Fig 1.—Time-series analyses of prescribing zomepirac sodium (bottom), other nonsteroidal anti-inflammatory drugs (NSAIDs) (top), and propoxyphene (hydrochloride or napsylate) (middle) among primary care physicians prescribing zomepirac (n=260) vs those prescribing NSAIDs other than zomepirac (n=308).

from the market, prescribing of other NSAIDs rose rapidly among former zomepirac prescribers to the rate observed in the comparison cohort.

We also compared monthly rates of prescribing of the other study analgesics between zomepirac prescribers and other NSAID prescribers. The presence of zomepirac on the market was associated with a clear divergence of trends between the two groups in the use of single-agent and combination propoxyphene products (Fig 1, middle). Prior to the release of zomepirac, future prescribers of zomepirac showed a slightly higher rate of prescribing propoxyphene than the comparison group. After zomepirac entered the market, the relative rates of propoxyphene use in these two groups reversed, with other-NSAID prescribers having a slightly but consistently higher preference for propoxyphene than zomepirac prescribers. When zomepirac was withdrawn, the rates of prescribing propoxyphene in the two groups became very similar.

The results of segmented linear regression models of analgesic preference are presented in Table 2. As shown in

Table 2.—Changes in Analgesic Preference Following Release of Zomepirac and Its Market Withdrawal Among Prescribers of Zomepirac and Prescribers of Other NSAIDs*

	Study Analgesic Category, Proportional Share of Use (SE)†				
	Zomepirac Sodium	Other NSAIDs	Propoxyphene‡	Other Opioids	Barbiturates
Use at beginning of study period (June 1980)	0.000	0.475 (0.0061)	0.210 (0.0042)	0.206 (0.0040)	0.109 (0.003)
Monthly trend in use (July 1980-September 1983)	<0.001§	0.002 (0.0003)	<0.001	-0.002 (0.0002)	<0.001
Changes in average monthly use among prescribers of other NSAIDs					
While zomepirac on market	<0.001	0.059 (0.0087)	-0.027 (0.0061)	-0.013¶ (0.0058)	-0.018# (0.0045)
Following withdrawal	<0.001	-0.023¶ (0.0010)	0.008 (0.0069)	0.033 (0.0066)	-0.018# (0.0051)
Difference between prescribers of zomepirac and prescribers of other NSAIDs					
While zomepirac on market	0.110 (0.001)	-0.081 (0.0047)	-0.028 (0.0033)	-0.002 (0.0031)	0.001 (0.0024)
Following withdrawal	-0.110 (0.003)	0.068 (0.0118)	0.021¶ (0.0082)	-0.005 (0.0078)	0.027 (0.0061)

*NSAID indicates nonsteroidal anti-inflammatory drug.

†Based on time-series regression models.

‡Propoxyphene hydrochloride or propoxyphene napsylate.

§SEs not reported for proportions <0.001.

||P<.001.

¶P<.05.

#P<.01.

Fig 2, during the period zomepirac was on the market (November 1980 through February 1983), the total preference for NSAIDs grew significantly in both groups of prescribers. However, among our cohort of zomepirac prescribers, we estimate that NSAID use (including zomepirac) was 2.9% higher than among other-NSAID prescribers (95% CI, 1.9% to 3.9%; $P<.001$). This difference in preference was balanced by a lower use of propoxyphene analgesics (-2.8%; 95% CI, -2.2% to -3.4%; $P<.001$) among zomepirac prescribers. The use of other opioid analgesics and barbiturates declined significantly in both groups.

After zomepirac was withdrawn from the market, over two thirds of the 11.0% of analgesic prescribing previously allocated to zomepirac was offset by a relative increase in the use of other NSAIDs (+6.8%; 95% CI, 4.4% to 9.2%; $P<.001$). Despite this increase, total NSAID use among zomepirac prescribers remained about 1.4% lower than in the comparison group. Relative increases in two other analgesic categories offset the remaining reductions in zomepirac prescribing. Preference for propoxyphene was 2.1% higher among former zomepirac users (95% CI, 0.4% to 3.8%; $P<.05$), and relative use of barbiturates was 2.7% higher (95% CI, 1.5% to 3.9%; $P<.001$). The use of other opioid analgesics rose significantly in both groups during this period.

COMMENT

Zomepirac and the Analgesic Market

We are not aware of any well-designed studies that have investigated the intended and unintended impacts of withdrawal of a drug by its manufacturer due to unexpected and serious adverse drug reactions.³⁰ Zomepirac was an interesting product to study because it captured a substantial share of the an-

algesic market very soon after it was introduced, and maintained this level consistently throughout its market life. In our large Medicaid claims database, zomepirac accounted for 12.4% of NSAID use while it was on the market, and 6.4% of total analgesic prescribing, findings that are reasonably consistent with national figures.³¹⁻³³

Zomepirac's rapid acceptance and large market share suggest an effective marketing effort by McNeil. Nationally disseminated mailed warnings to prescribers in April 1982 concerning zomepirac's potential to cause anaphylactic reactions had no detectable effect on zomepirac use in our cohort of 260 zomepirac prescribers, or in the larger cohort of 1964 physicians. One explanation for the warning's apparent lack of impact was the launch of a major promotional campaign targeting zomepirac prescribers 1 week after the mailed letter. It is possible that the apparent overall lack of effect of product warnings, rather than reflecting a stable market, may mask a situation in which some physicians reduced prescribing due to concerns about the product, while others increased prescribing in response to intensified marketing efforts.

Regardless of the promotional campaign's effectiveness, mailed warnings about pharmaceutical products have been shown to be very weak behavior-change interventions in comparison with more direct, person-to-person methods.¹ We previously reported a similar lack of effect of repeated warnings by the US Food and Drug Administration and pharmaceutical manufacturers aimed at reducing misuse of propoxyphene analgesics due to their risk of toxic effects and habituation.²¹

There is ample evidence that zomepirac's entry into and exit from the marketplace was accompanied by significant

shifts in choice of analgesic therapies. Primary care physicians were the predominant prescribers of zomepirac. When zomepirac became available, it appears to have been adopted by some primary care physicians not only as a preferred NSAID, but also as an apparently safer, more rational alternative to analgesics such as propoxyphene for treating general acute or chronic pain.³¹ When zomepirac was withdrawn, the majority of its use was replaced by other NSAIDs, an apparent gain in product safety. However, significant increases in preference for propoxyphene and fixed-combination barbiturate analgesics were also seen. These substituted products themselves carry notable risks of adverse clinical consequences, including habituation and accidental death.

Limitations of Study Methods

Several limitations of our methods and threats to the validity of our findings must be considered. The generalizability of our results may be limited by a number of factors. Our sample selection process eliminated any physician who did not prescribe at least one analgesic to a member of our random sample of patients. We also observed only the Medicaid portion of each study physician's practice, and we further required that physicians have some analgesic prescribing for the entire duration of the study. The relatively small sizes of the Medicaid practices for many physicians made analysis at the physician level impossible. However, the distribution of use of individual NSAIDs in our analyses closely approximates the patterns observed in a representative national sample of computerized pharmacies.³¹ There is no reason to believe that the prescribing habits of our study cohort differ significantly from the habits of physicians who did not meet the require-

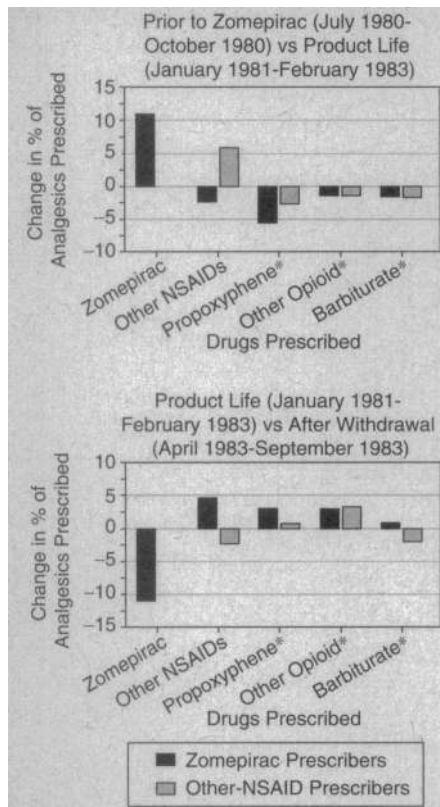


Fig 2.—Changes in preference for selected categories of analgesics among prescribers of zomepirac sodium (n=260) and prescribers of nonsteroidal anti-inflammatory drugs other than zomepirac (n=308) both following the release of zomepirac (top) and after it was withdrawn from the market (bottom). The drugs marked with an asterisk are analgesic preparations containing propoxyphene hydrochloride, another opioid, or a barbiturate.

ment for prescribing activity in Medicaid, or that their prescribing habits would vary for the larger, non-Medicaid portion of their practices.

We were only able to obtain data on analgesic prescribing for 4 months prior to the release of zomepirac, and 6 months following its withdrawal from the market. Consequently, longer-term trends in the prescribing of competing analgesic products, independent of changes associated with zomepirac's entry into and withdrawal from the market, were difficult to detect. However, because of the rapid rise in the popularity of zomepirac and its sudden withdrawal, short-term changes in prescribing habits were clearly discernible.

Other methodological problems arise from the quasi-experimental nature of the study design. Interrupted time-series analysis, the strongest statistical technique for analysis of nonexperimental data, may not detect subtle changes in trend, and cannot conclusively determine the reasons for observed changes. We compensated for this deficit by in-

cluding a comparison group of other-NSAID prescribers. However, we had no control over which primary care physicians were classified as zomepirac prescribers or other-NSAID prescribers. Our cohorts of zomepirac prescribers and other-NSAID prescribers differed slightly at baseline in rate of analgesic use in their practices. Other-NSAID prescribers may also differ in other ways; for example, they may be less likely to try new analgesic products, or they may see a different mix of patients and, therefore, use different medications. However, although differences between these two groups are likely to exist, the overall similarity of patterns of analgesic use before zomepirac was first marketed, the stability of prescribing throughout the study period, and the visible discontinuities in use of specific drugs following the changes in the marketplace give credibility to the measured substitution effects.

Could the observed changes in drug use be explained by other changes in the marketplace? Divergence of the utilization trends for zomepirac and other-NSAID prescribers immediately following the market entry of zomepirac and the sudden convergence of trends in certain substitute categories following the market withdrawal of zomepirac make it very unlikely that unrecognized factors were responsible for these substitution effects.

Because of the retrospective nature of the study and limitations on available data, it is impossible to assess certain characteristics of the study physicians that might influence their reactions to product withdrawals. For example, we know little about case-mix profile, specific motivations for choosing zomepirac vs alternative analgesic products, or the influence of patient requests for particular types of analgesic. To truly understand the dynamics of prescribing behavior, one would have to characterize prospectively these and other clinical and nonclinical factors.³⁴

Understanding Product Risks and Benefits in Context

Some drugs have substantial risks that are tolerated because of their established benefits in relation to available therapeutic alternatives (eg, zidovudine). However, even less toxic drugs do not always prove safe or effective for every individual. From the epidemiologic rather than the clinical perspective, prescribing following a regulatory change or product withdrawal becomes relatively safer if the combined statistical risk of all products prescribed within a therapeutic category decreases.

Recent examples exist of the banning

or voluntary withdrawal of pharmaceutical products thought to be unsafe or ineffective.⁴ Although limited, the best available data suggest that the quality of prescribing can either increase or decrease following the removal of specific medications from a national formulary³⁵ or the withdrawal of Medicaid reimbursement for scientifically unsubstantiated therapies.⁴ One study reported no reduction in risk of self-poisoning when dangerous products implicated in drug abuse were removed from the national market, primarily because of increased abuse of drugs of equal or greater toxicity.¹⁷ Thus, suboptimal product substitution following well-intended regulatory initiatives seems to be a generalized phenomenon that policymakers must consider whenever restrictions on drug availability are proposed.

Risk trade-offs due to product substitutions can occur not only when drugs are banned or withdrawn, but whenever prescriber choices are constrained, whether by economic or administrative limits. Even less drastic interventions, such as audited triplicate prescription forms for benzodiazepines, have been associated with undesirable substitution effects.³⁶ Decision makers should carefully consider the relative risks of competing products when determining pharmaceutical coverage policies in all settings that maintain formularies or otherwise restrict access to specific products, from major federal programs (eg, Medicare, Medicaid, and the Department of Veterans Affairs) to individual health organizations.

This study examined a product to which significant, dramatic, and immediate health risks were ascribed. Approximately 40 deaths were attributed to anaphylactic reactions to zomepirac in the Food and Drug Administration's Sentinel Reporting System in the 28 months it was on the market³⁷; a revised Food and Drug Administration estimate totaled 14 zomepirac-related deaths.¹⁰ Based on data from 1982 and early 1983,^{31,32} about 15 million prescriptions for zomepirac were written while it was on the market. Taken together, these estimates indicate a total risk of 0.9 to 2.7 deaths per million zomepirac prescriptions. Thus, substitution of other NSAIDs, which have a far lower risk of anaphylaxis,¹⁵ for zomepirac may represent safer prescribing.

However, propoxyphene and barbiturate-containing analgesics, which we have shown to be competing therapeutic substitutes for zomepirac, also carry risks. For example, it has been estimated that there are approximately 50 deaths per million propoxyphene prescriptions, about 40% of which were attributable to

overdose during our observation period.³⁸⁻⁴⁰ Propoxyphene and barbiturates are also associated with other nonfatal adverse outcomes, including habituation.²¹ However, these drugs' risks are less dramatic than zomepirac's, are less likely to be reported, and are therefore less visibly attributable to the products in question.

We did not have access to morbidity and mortality data necessary to conduct a reliable population-based risk analysis. However, the key policy lesson to be learned goes beyond the important issue of whether zomepirac's withdrawal from the market was associated with an increase or decrease in drug-related mortality. How could market withdrawal have been better accomplished? Educating prescribers about appropriate pain management remains a long-term strategy for decreasing analgesic risks, but such education is time-consuming and difficult to operationalize.¹ At a mini-

mum, this study highlights a need for more effective communication to medical practitioners before or during product withdrawals or regulatory changes to alert them to both the drug removal and preferred therapeutic alternatives.⁴ Since mailed circulars appear to be ineffective means to accomplish these tasks, other strategies need to be explored, perhaps using credible opinion leaders or local medical associations as communication channels.

In summary, one cannot evaluate the impact of withdrawing a given drug associated with serious adverse drug reactions except in relation to the risks posed by substituted products. Although policymakers may assume that withdrawing a drug eliminates its entire burden of risk, this is certainly not the case. This study underscores the need for policymakers to consider risk in context and to anticipate unintended drug substitutions. Physicians respond actively, not

passively, to forced changes in their range of therapeutic options. The degree of improvement in quality of care through drug-restriction policies depends on the characteristics of available therapeutic alternatives, the perceptions of prescribers and patients toward those alternatives, and the degree to which timely education and promotional efforts can influence prescribing. At the very least, a growing body of literature suggests that private and public policymakers should identify likely effects of rational and irrational product substitution before banning specific agents in order to characterize, and hopefully prevent, unintended outcomes.

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