Effect of Government and Commercial Warnings on Reducing Prescription Misuse: The Case of Propoxyphene

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Abstract: We analyzed trends in prescribing and overdose deaths related to propoxyphene (e.g., Darvon) before and after a 1978–80 informational campaign carried out by the US Food and Drug Administration and the drug's manufacturer through mailed warnings, face-to-face education of prescribers, press releases, and labeling changes. The goals included a reduction in propoxyphene use with alcohol or other CNS depressants, reduced prescribing of refills, and cessation of prescribing for patients at risk of abuse and misuse (suicide).

We conducted time-series analyses of nationwide propoxyphene use data 1974–83 and analyzed data on drug overdose death rates covering a combined population of about 83 million. Segmented regression methods were used to determine if the informational program was associated with changes in trends of prescribing or overdose deaths. Comparison drug series were analyzed to control for other secular trends in prescribing.

Nationwide propoxyphene use during the warnings continued a pre-existing decline of about 8 per cent per year, but this decline halted after the warnings. The no-refill recommendation had no impact on refill rates. The risk of overdose death per propoxyphene prescription filled has remained about constant since 1979. Sharper declines in misuse of such drugs will require stronger, more sustained regulatory or educational measures. (*Am J Public Health* 1987; 77:1518–1523.)

Introduction

It occasionally becomes necessary to limit use of a particular prescription drug because of new data pointing to toxicity or other problems in certain settings. Short of withdrawing the drug from the market altogether, a variety of regulatory and voluntary options exist to limit the use of such a medication to specific clinical situations. The case of propoxyphene offers the opportunity to study the use of one such medication as it was subjected to a variety of interventions aimed at reducing its misuse.

Propoxyphene (Darvon, Darvocet, Wygesic, etc.) is a prescription analgesic which, despite its popularity, has been reported to have efficacy at best comparable to aspirin or acetaminophen, and with risk of overdose and habituation.[1,2] From 1978 to 1980, the US Food and Drug Administration (FDA) and the main manufacturer of propoxyphene attempted to reduce overdose deaths through an educational program of mailed warnings to physicians and pharmacists, labeling changes, and manufacturers' person-to-person education through their sales force. The goals of this program included the prevention of concurrent use of the drug with alcohol or other central nervous system (CNS) depressants, reduced prescribing for high-risk (e.g., suicidal or depressed) populations, and reduction in unnecessary refills. These efforts in turn were covered extensively by the media.

Acronyms Used

FDA, US Food and Drug Administration
DEA, Drug Enforcement Administration
IMS, IMS America, Ltd.
NPA, National Prescription Audit (carried out by IMS)
NDTI, National Disease and Therapeutic Index (by IMS)
DAWN, Drug Abuse Warning Network
SMSA, standard metropolitan statistical area
NSAIDs, non-steroidal anti-inflammatory drugs

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Little information exists on the extent to which such activities can improve inappropriate prescribing in outpatient practice. Several uncontrolled observational studies conducted in Sweden and the United Kingdom[3–5] have associated government warnings concerning the toxic effects of dipyrone, chloramphenicol, and pressurized aerosols with reductions in their use and associated morbidity and mortality. However, these products produced adverse effects of great toxicity, and it is difficult to separate out the influence of widespread media reports and concurrent marketing ("detailing") of competitors' products to replace these drugs. Two recent controlled trials in the US[6,7] failed to detect changes in the appropriate prescribing of propoxyphene, peripheral/cerebral vasodilators, and several antibiotics among a sample of office-based physicians receiving mailed print materials alone; however, face-to-face educational visits ("academic detailing") sponsored by a state medical society or a medical school, in combination with printed materials, were successful in changing prescribing practices in both studies.

Government/Private Activities

Propoxyphene was introduced by Eli Lilly and Company in 1957 as a prescription analgesic indicated for mild-to-moderate pain. Although it was first marketed as a non-narcotic drug as effective as codeine, later evidence from well-controlled clinical trials indicated that pure propoxyphene (e.g., Darvon in standard doses) is no more effective than and possibly inferior to plain aspirin or acetaminophen as an analgesic.[1,8–10] Most studies suggest that combinations of propoxyphene and aspirin or acetaminophen are probably roughly equivalent in efficacy to the over-the-counter products alone.[1,2] However, propoxyphene lacks the anti-inflammatory properties of aspirin and other non-steroidal anti-inflammatory agents introduced in the mid-1970s. Nevertheless, effective marketing of this drug combined with physicians' and patients' perceived need for an intermediate product between aspirin and the narcotics led to high use of the various agents containing propoxyphene.

In the 1960s and 1970s, numerous reports began to appear of addiction and both intentional and unintentional overdoses with propoxyphene, particularly when combined

with alcohol or other drugs.[2,11,12] Although the drug is structurally related to the opiates, the majority of overdose cases were confined to medical populations rather than illegal drug abusers.[12] By 1977, propoxyphene ranked second only to the barbiturates as the leading agent implicated in prescription drug-induced deaths in the US, causing an estimated 1,000–2,000 overdose deaths per year, sometimes at doses only slightly higher than normal therapeutic ranges when combined with alcohol or other sedatives.[13] Because of the growing problem of abuse, in 1977 the Administrator of the Drug Enforcement Administration (DEA) included propoxyphene products in Schedule IV of the Controlled Substances Act. In the spring of 1978, the FDA issued an article through the FDA Drug Bulletin notifying physicians for the first time of the possibility of accidental deaths associated with propoxyphene.[13]

In November 1978, the consumer advocacy group, Public Citizen, petitioned the DEA to reschedule propoxyphene-containing products to Class II under the Controlled Substances Act, which would impose production quotas and prohibit refill and telephone prescriptions. Simultaneously, it asked the Secretary of the Department of Health, Education, and Welfare (HEW) to ban the marketing of propoxyphene immediately as an "imminent hazard." After several widely publicized congressional hearings on the subject of propoxyphene abuse in early 1979, HEW and DEA rejected such severe regulatory restrictions and embarked on promoting educational programs designed to improve the safe use of propoxyphene voluntarily.

Because FDA had no ongoing physician education program of its own, it required manufacturers of propoxyphene to revise the drug's labeling and conduct both a mailed and person-to-person educational campaign, conveying the following messages to physicians, patients, and pharmacists:

- do not prescribe propoxyphene to high-risk groups (suicidal, abuse-prone, or addiction-prone patients); and
- do not combine alcohol, tranquilizers, or sedative-hypnotics with propoxyphene.

These messages were sent to 145,000 physicians in mailed warnings produced by the major manufacturer of propoxyphene, Eli Lilly and Company.[14] They were also required as boxed warnings in advertisements and in the Physician's Desk Reference, and were recommended for use in patient package inserts. The FDA included these recommendations in headlined reports contained in two FDA Drug Bulletins in the spring and fall of 1979[13,15] which were mailed to most physicians in the country.

Since face-to-face persuasion by drug company sales representatives (detailers) was thought to be the most powerful influence on prescribing behavior, Eli Lilly also agreed to communicate the above warnings in person-to-person marketing activities devoted solely to education about propoxyphene risks. Their plans included visits to 125,000 physicians who were heavy Darvon prescribers. By the spring of 1980, an audit/investigation conducted by the FDA used detailed descriptions of these visits to determine the level of compliance with FDA's requirement that such sessions be used to provide information on propoxyphene risks. Following this investigation, an FDA official concluded that the principal manufacturer of propoxyphene (Eli Lilly) had "not met its commitment for a personal contact informational campaign intended solely to sensitize prescribers and dentists to the precautions necessary for safe use of propoxyphene products."[16] By the third and fourth months of the campaign, the FDA found that less than 10 per cent of the details conveyed suitable information on the new warnings; over 75 per cent of detailers left free samples of Darvon products. The official quoted several verbatim messages from Lilly detailers recorded by physicians: "Darvon and Lilly won FDA battle"; "Safe in spite of Nader report"; "OK by Drug Commission"; "Few if any side effects."[16] The FDA had also urged the company to eliminate sales commissions for Darvon products to reverse an economic incentive on the part of the sales force to promote Darvon use.

In an effort to further reduce the easy availability of propoxyphene to high-risk populations, in mid-1980 the FDA recommended that all physicians write "no refill" on propoxyphene prescriptions and order all propoxyphene prescriptions in writing rather than by phone. This suggestion was essentially a voluntary request that physicians behave *as if* the drug had been rescheduled to Category II of the Controlled Substances Act. If followed, this would have been much more comprehensive in its effect than the warnings for high-risk groups above. This recommendation was headlined and discussed in the July 1980 issue of the FDA Drug Bulletin[17] mailed to physicians throughout the country, and was also the subject of widespread media attention.[18] Lilly publicly criticized the no-refill recommendation, maintaining that it would create unnecessary burdens for physicians and patients.[19] The consumer advocacy group also denounced this voluntary measure but for a different reason, arguing that the program was inadequate to deal with the problems of propoxyphene overdose and addiction.

Media reports of the Public Citizen petitions, public hearings, FDA regulatory actions, and company responses could also have influenced patient and physician demand for propoxyphene. A search of the National Newspaper Index, covering 23 cities during the period from 1979 to 1986,[20] indicates that all reports mentioning propoxyphene (or Darvon) and risk or warnings occurred during 1979 (16) and 1980 (7).

Research Questions

Were the combined government/commercial educational activities and accompanying press reports effective in altering prescribing patterns of physicians and reducing overdose deaths involving propoxyphene? In response to a request to the Secretary of Health and Human Services to monitor and evaluate the success of these voluntary efforts, several FDA reports were produced from late 1979 to July 1981 to examine trends in propoxyphene use and abuse.[21–23] However, not enough years of follow-up data (e.g., only six months of overdose data beyond the final warnings), nor statistical adjustments of pre-existing trends, were provided to adequately evaluate the success of the educational efforts. In the present analysis, this report was supplemented by more complete data from several other sources, in order to address the following issues:

- Was there a decrease in the nationwide trend of propoxyphene use during and after the information campaign? If so, how long did these changes persist?
- Did physicians become more selective and careful in their use of propoxyphene to reduce risk? For example, was there a reduction in refill versus new prescriptions after the no-refill warning? Were there changes in dose per prescription? Were high-risk patients less likely to receive propoxyphene after the information campaign?
- Were the warnings followed by a reduction in the

number of propoxyphene-related overdose deaths, controlling for the overall number of prescriptions dispensed?

Methods

Research Design

We used the interrupted time series with comparison series,[24] to estimate the impact of the informational campaign on physician prescribing behavior and overdose deaths. This design is particularly appropriate for analyzing the effects of nationwide educational or regulatory activities for which random assignment is unethical or not feasible. For each of the settings and variables of interest (see below), we observed trends in prescribing of propoxyphene before, during, and after the warnings, to determine whether the interventions were associated with changes in these outcomes over time. We also analyzed changes in the use of non-targeted drugs to control for other historical factors which could also have contributed to observed changes in the outcome variables.

Prescribing Variables and Data Sources

Nationwide Propoxyphene Use—To examine nationwide changes in propoxyphene use we analyzed data provided by the FDA[25] estimating the total yearly number of all propoxyphene-containing prescriptions purchased in retail pharmacies in the continental United States from 1974–83. These data were obtained from IMS America's National Prescription Audit (NPA), an ongoing study of a large representative sample of 1,200 retail pharmacies.[26] The methods and quality of these data have been described more fully elsewhere.[27,28] Similar data were obtained for all non-steroidal anti-inflammatory drugs (NSAIDs)[29] to control for other changes in the marketplace for analgesics which could have affected propoxyphene use.

Propoxyphene Refills and Selectivity of Use—The FDA's fifth quarterly report (described above)[23] contained NPA data on the total number of new versus refill prescriptions by quarter in the US from late 1978 to early 1981 (about nine months after the no-refill recommendation), as well as data on dose per prescription, and age and sex distributions of propoxyphene users over time, based on IMS America's National Disease and Therapeutic Index (NDTI).[30] Since overdose or abuse cases were more likely to occur among younger age groups, this made it possible to determine whether prescribing for this group was differentially affected.

Overdose Deaths

To track overdose deaths for propoxyphene, we obtained data from the National Institute on Drug Abuse on overdose deaths associated with the medication as reported in the Drug Abuse Warning Network (DAWN) from July 1977 to June 1983.[31–33] These data are collected to monitor all drug abuse deaths identified by a panel of medical examiners in approximately 27 standard metropolitan statistical areas (SMSAs) representative of the nation as a whole, covering approximately one-third of the US population. We included in our analyses only those 22 SMSAs which continuously reported data from 1977 to 1983, and which covered a total population of approximately 50 million in 1978.

In addition, we obtained annual data on overdose deaths over the same period from a study by Finkle[34] which used uniform criteria to identify in a population of 56.5 million all well-documented overdose cases in which the pathologist and toxicologist believed that propoxyphene was an important causative factor. Previous reports have found this

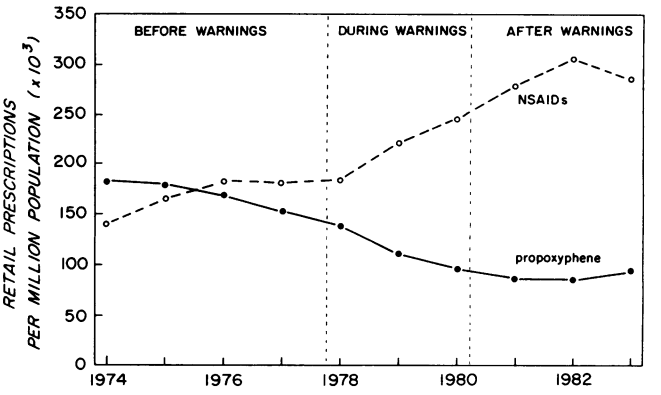

FIGURE 1—Prescriptions for Propoxyphene-containing Products versus Non-steroidal Anti-inflammatory Drugs (NSAIDs) Dispensed by Retail Pharmacies in the US from 1974–1983
Data provided from US FDA, based on National Prescription Audit.[25,26] Slope of regression line before warnings was −15,704 propoxyphene prescriptions per million population per year (SE = 2,542); change in slope during warnings (NS) was −404 (SE = 3,995); change in slope during 1981–83 was +12,499 (SE = 4,681).

measure to be sensitive in detecting practically significant changes in trend over time.[27]

Data Analysis

Time-series regression models were fit to test whether the period of FDA warnings was associated with a departure from pre-existing trends of propoxyphene use. Segmented regressions were specified to model pre-, during-, and post-warning changes in trend.[35] Regression coefficients were estimated assuming first order autocorrelated errors using the two-step full transform method.[36,37] Where appropriate, standard errors of these coefficients were provided to indicate the precision of estimated changes in trend.

Results

Nationwide Propoxyphene Use

Figure 1 documents a pre-existing downward trend in US propoxyphene use of about 8 per cent per year beginning in 1975 which continued unchanged during the period of most intense informational activity occurring from 1978–80. In fact, the time-series demonstrated a flattening out of this downward trend beginning in the post-warning period. This change in trend (12,500 prescriptions more per million population per year) was almost as great in magnitude as the prior rate of decline had been (Figure 1). In 1983, there were an estimated 22 million retail prescriptions of propoxyphene in the US. The rapid proliferation, marketing, and subsequent use of new NSAIDs (Figure 1) and later stabilization in growth of these competitive products may partially explain the changes in propoxyphene trends observed. However, since the informational campaign addressed only specific uses of propoxyphene and did not attempt to eliminate use of the drug altogether, analysis of total prescriptions dispensed may not be sensitive enough to measure the effect of the warnings. Therefore, we conducted additional analyses to investigate the specific impact of the no-refill warnings.

Effect of Warnings on Propoxyphene Refills and Dosages

Figure 2 presents time-series data on the percentage of total prescriptions which were refills in the eight quarters before and three quarters after the no-refill warning. There was no change in refill rates over time; in fact, this rate was remarkably stable with a mean of 43 per cent (SD = 1.4)

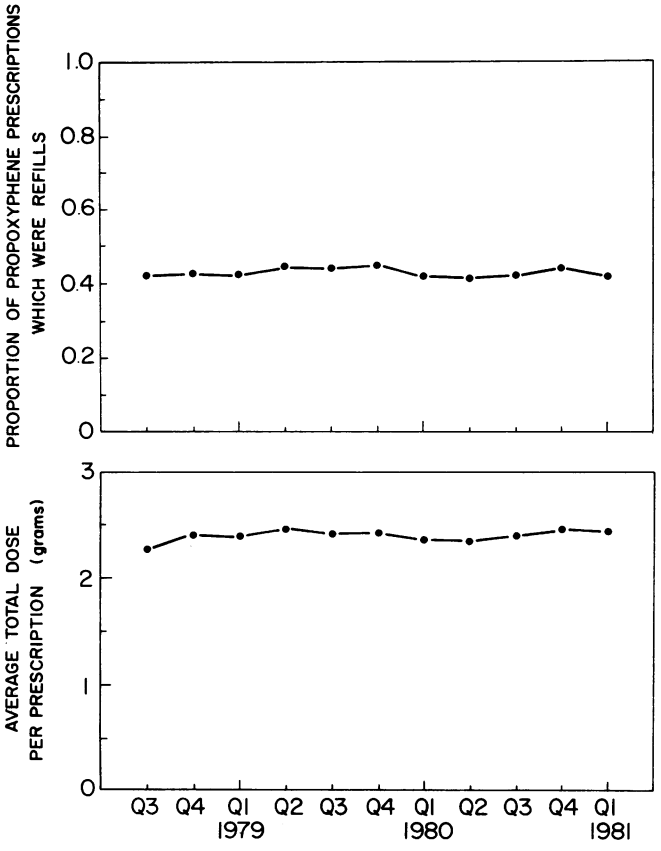

FIGURE 2—Trend in Propoxyphene Refill Rates (top half) and Dose per Prescription (bottom half) Dispensed by Retail Pharmacies in the US by Quarter from July 1978 through March 1981
Data provided from US FDA, based on National Prescription Audit.[23,26]

throughout the period. The time-series analysis also failed to detect even small shifts in the average number of grams per prescription which remained stable at approximately 2.4 grams (SD = 0.05) during and after the warnings (Figure 2). There were also no changes in the age and sex distributions of propoxyphene recipients from the second quarter of 1979 to the first quarter of 1981.[23] Throughout this period approximately two-thirds of recipients were women, and about 35 per cent were below age 40.

Propoxyphene Overdose Deaths

Figure 3 presents time-series data on the number of propoxyphene-related overdose deaths in Finkle's study sites from 1977 to 1982[34] and in the DAWN system (July 1977–June 1983) per million prescriptions dispensed. While Finkle's data suggest a downward trend in rates of medical examiner mentions per million prescriptions until 1979, both trends showed no further progress in death rates since that time. Since 1979, the average yearly number of deaths per million propoxyphene prescriptions was 56 (SD = 3.0) in the Finkle study sites, and 48 (SD = 1.7) in the 22 DAWN SMSAs. We also plotted separate trends for 11 overlapping counties in the two data sets. The trends from the two sources were almost identical, thus validating the DAWN data system.

Figure 4 presents data on the relative rates of relinquishment (in rank levels) of the leading individual propoxyphene products. If physicians were reducing propoxyphene use due

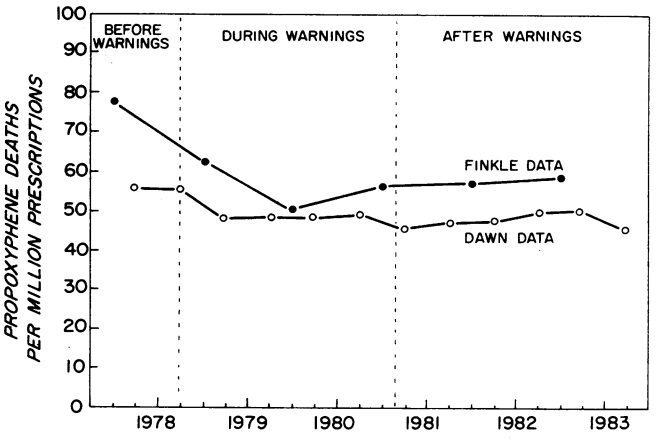

FIGURE 3—Trend in Propoxyphene-related Deaths per Million Propoxyphene Prescriptions Dispensed by Half-year Periods among 22 consistently Reporting SMSAs in the Drug Abuse Warning Network (July 1977–June 1983); and by Year in Finkle's 26 Study Sites (1977–1982)[34]
The denominator of propoxyphene prescriptions dispensed is based on IMS data for the nation as a whole,[26] adjusted to reflect the proportion of the US population covered by the study sites (23%, and 26%, respectively).

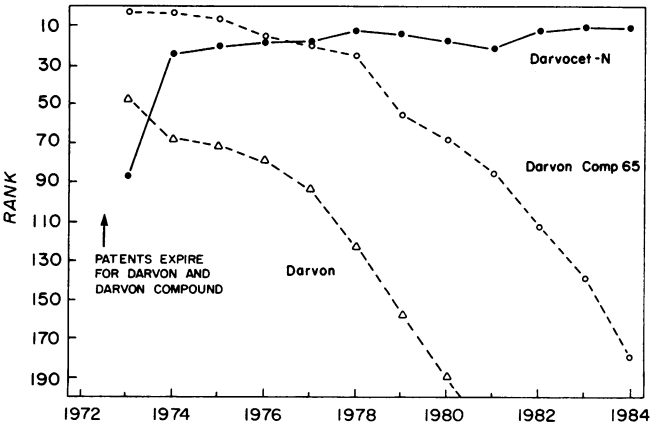

FIGURE 4—Twelve-year Trend (1973–84) in Market Position (rank) of Most Popular Propoxyphene Products among the Top 200 Drug Products Nationwide (based on data from the National Prescription Audit[38–49] of retail pharmacies)

to increasing awareness of toxicity, one would have expected an even decline in use of the various propoxyphene products, since all have relatively equal toxicity potential. In contrast, a competing hypothesis would show a greater decline in those propoxyphene products which were no longer being marketed forcefully, since their patents had expired. As shown in Figure 4, the data fit much more closely with the competitive commercial marketing hypothesis. As several non-steroidal anti-inflammatory agents rose rapidly in market position (see Figure 1), use of propoxyphene hydrochloride (e.g., Darvon) and propoxyphene with aspirin (Darvon Compound-65), both of which were available generically in 1973, began to decline rapidly. However, the popular combination of propoxyphene napsylate with acetaminophen, which was still under patent (Darvocet-N), maintained or improved its market position through 1984. Further suggestive data supporting the competition/substitution hypothesis is provided by the fact that when the non-steroidal anti-inflammatory drug zomepirac (Zomax) was withdrawn from the market because of toxicity, Darvocet-N's market position rapidly increased from the 20th rank in 1981 to the 10th ranked drug in 1983.

Discussion

This analysis suggests that use of propoxyphene during the period of government and commercial warnings did not depart from a pre-existing downward trend of about 8 per cent per year. In fact, this trend stabilized in the post-warning period. It is conceivable that the pre-existing downward trend might have ceased in the absence of the warnings, which may have perpetuated it. While we cannot rule out this possibility, the lack of impact on other aspects of propoxyphene use (e.g., refills, patient demographics) make this alternate explanation less likely. Despite having sufficient statistical power to detect a change in slope of 0.27 per cent per quarter in refill prescribing of propoxyphene at the $p = .05$ significance level, we found no evidence of any temporary or permanent effects of the no-refill campaign. Nor were there any changes in dose per prescription, or in the age and sex distribution of patients to whom the drug was prescribed. In the time-series analyses, R^2 statistics were generally above .9 (except for the flat trend lines in Figure 2 which indicates no change from the mean over time), indicating that the segmented regression models fit the data well. Controlling for the overall number of prescriptions dispensed in the US, both the Finkle data[34] and our analysis of data from the DAWN system indicate that the risk of propoxyphene-related deaths have remained constant since about 1979 at approximately 52 deaths per million prescriptions dispensed, or about 1,100 deaths per year in the US. Since the major messages in the 1979 warnings strongly urged more selective use of propoxyphene, the lack of change in risk of death per prescription since 1979 suggests a failure of this aspect of the campaign. In 1983, the number of DAWN system deaths associated with propoxyphene (261) was only slightly lower than the estimated frequency of cocaine-related deaths (314).[50]

Several limitations of these analyses need to be considered. First, aggregate data can not address such difficult-to-measure outcomes as reduced prescribing for suicidal or depressive patients. Second, it may be possible that the stabilization in use reflects the resistance of a "hard core" of propoxyphene recipients who were addicted or otherwise demanded that the drug be continued. In earlier prescribing research,[6] many physicians reported that patient demand for propoxyphene was frequent and hampered attempts to substitute other analgesics. Pre-existing downward trends in propoxyphene use and abuse may be partially explained by the appearance and vigorous promotion of the new class of non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin). The most popular NSAIDs were first introduced and heavily marketed in the 1970s for many of the same indications as propoxyphene products. Any examination of the impact of federal warnings on propoxyphene use must consider this possible substitution effect. Four NSAIDs rapidly rose to the top 100 prescribed products during the study period: ibuprofen (Motrin) in 1975; naproxen (Naprosyn) in 1977; sulindac (Clinoril) in 1979; and zomepirac (Zomax) in 1981.[42,44,46,48]

The above data suggest that the extent of propoxyphene use is related most importantly to its overall popularity in relation to competitive products, probably influenced in large part by effective marketing activities. The warning campaign had little impact on reducing the way propoxyphene was prescribed. The frequency of overdose deaths correlates primarily with the overall availability of propoxyphene in the population (Figure 3) rather than with the selectivity of its use. These data also imply that further declines in propoxyphene overdose deaths would require stronger and more sustained measures, such as more stringent regulation or non-commercial, objectively based educational "detailing"[6,7] (see below).

Previous studies provide both empirical and theoretical support for the observations presented. First, two controlled trials covering five states[6,7] have shown that print-alone educational materials are often not effective in changing physician behavior in outpatient practice. These findings are further supported by a recent review of pharmaceutical education experiments in the hospital setting,[51] and a randomized trial of a mailed continuing education program in antihypertensive care.[52] A 1972 survey supported by the FDA[53] found that physicians reported being generally satisfied with its Drug Bulletin as an information source; 42 per cent reported reading at least portions of interest; and 36 per cent reported that it influenced their behavior. However, in the case of propoxyphene, physician self-reports regarding sources of information and prescribing beliefs and behavior may not correlate with actual practice.[54] Eliminating refill prescriptions of a popular drug and prescribing differentially for high-risk patient populations are complex behavioral changes which may require more sophisticated education programs that are based on physicians' actual motivations for using specific medications.[51] For example, two randomized controlled trials have found that medical school based educators meeting with physicians in their offices could bring about a significant decrease in inappropriate use of several drugs, including propoxyphene.[6,7] In one study, a formal benefit-cost analysis revealed that this approach actually saved far more dollars than it would cost to conduct.[55]

Careful use of ongoing federal data collection systems are also needed to estimate time trends in utilization and adverse effects to form a more reliable basis for evaluating efforts to reduce unnecessary drug-induced morbidity and mortality. Experience from situations such as the propoxyphene-warning case can serve as models to understand the dynamics of physician adoption or relinquishment of health care technologies, and as such can begin to provide data to guide future efforts in this increasingly important area.

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