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The Impact of the Addition of Naloxone on the Use and Abuse of Pentazocine

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Synopsis

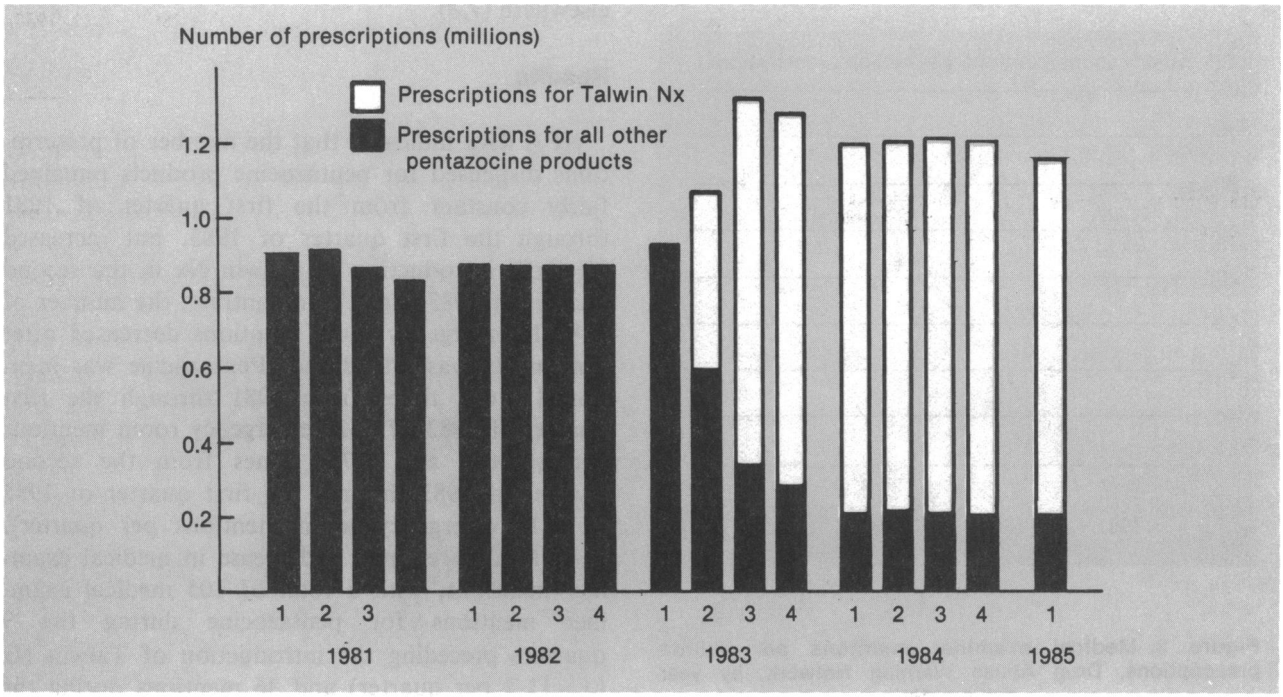
An epidemic of abuse with "T's and blues" began in the late 1970's in which pentazocine—Talwin tablets ("T")—and the antihistamine tripelennamine (known as blues) were crushed, dissolved together, filtered, and injected intravenously. The resulting high was reported to be similar to that of heroin. In 1981, the manufacturer and the Food and Drug Administration met to discuss a possible solution. As a result, 0.5 mg of naloxone hydrochloride, a narcotic antagonist that is pharmacologically inactive at that dose orally but active if administered parenterally, was added to the tablet formulation. The reformulated product, Talwin Nx, was approved for marketing in late 1982 and introduced in the second quarter of 1983. Distribution of Talwin tablets in the United States was discontinued.

The Drug Abuse Warning Network (DAWN) of the National Institute of Drug Abuse and IMS America's National Prescription Audit were used to review the use and abuse patterns of pentazocine before and after the naloxone intervention. The number of prescriptions dispensed quarterly for pentazocine products remained fairly stable from 1981 through the first quarter of 1983 and increased after the introduction of Talwin Nx. In contrast, DAWN emergency room and medical examiner mentions decreased after the product reformulation. The rates of both emergency room and medical examiner mentions per million prescriptions were substantially lower in the 2 years following the introduction of Talwin Nx (decreases of 70 percent by emergency rooms and 71 percent by medical examiners), indicating that the product reformulation successfully reduced pentazocine abuse.

IN 1967, INJECTABLE AND ORAL FORMS of pentazocine (Talwin) were approved for marketing by the Food and Drug Administration (FDA) as nonnarcotic analgesics indicated for the treatment of moderate to severe pain. Pentazocine had no known potential for abuse at that time, with the 1965 session of the World Health Organization's Expert Committee on Dependence-Producing Drugs having concluded that pentazocine was not likely to be abused, presented no significant risk to the public health, and need not be placed under narcotics control (*1*). However, the first reports of patient dependence on pentazocine were received in 1968. Pentazocine was initially thought to be abused only by a restricted patient population, but it soon became apparent that the drug was being more widely misused (*2*).

Pentazocine abuse became a significant public health problem in the latter half of the 1970s with the advent of "T's and blues" abuse. Talwin tablets (the "T") and the antihistamine tripelennamine (commonly available as a blue tablet) were dissolved together, filtered, and injected intravenously. The resulting effect was said to be similar

Figure 1. Number of prescriptions dispensed from retail pharmacies for pentazocine-containing products, by year and quarter



to that of heroin. Despite regulatory actions such as the 1979 listing of pentazocine under Schedule IV of the Federal Controlled Substances Act and control measures taken at the State level, abuse of T's and blues, both as a heroin substitution and a primary drug of choice, had reached epidemic proportions by the end of the 1970s (*3–5*).

Sterling-Winthrop (now Winthrop Breon), the manufacturer of pentazocine, met with FDA in 1981 to discuss a possible remedy: replacing oral Talwin with a new product that would be formulated by adding 0.5 mg of naloxone HCl, a narcotic antagonist, to the Talwin tablet. At this dose, naloxone is pharmacologically inactive when taken orally; however, if injected intravenously, it will block or reverse the narcotic effects of pentazocine or any agonist of the morphine receptor.

The combination pentazocine-naloxone product was approved by the FDA in late 1982 under the tradename Talwin Nx. In January 1983, the manufacturer stopped distributing single-entity Talwin tablets in the United States, and the first prescriptions for Talwin Nx were dispensed 3 months later.

The current study was designed to assess changes in the use and abuse of pentazocine in the 2 years after Talwin Nx was marketed. Conceptually, one would expect the addition of naloxone to reduce abuse greatly; however, there was little published research to confirm or refute this expectation. One study of drug abuse data for St. Louis, MO, did find a substantial reduction in pentazocine abuse as measured by several indicators during the year following the introduction of Talwin Nx (*6*).

Methods

Data were obtained from two sources: the National Prescription Audit (NPA) and the Drug Abuse Warning Network (DAWN). The NPA, generated by IMS America, is based on a panel of 1,200 computerized pharmacies and provides national estimates of the number of prescriptions dispensed from retail pharmacies in the conterminous United States. NPA data on the number of prescriptions dispensed each quarter from 1981 through the first quarter of 1985 were obtained for Talwin Nx and all other pentazocine products (including combination and injectable products). In 1983, IMS revised the methodology by which it extrapolates sample data, so changes from 1982–83 must be interpreted with caution; however, pentazocine data for the first quarter of 1983 were comparable to prior quarters.

The DAWN system, sponsored by the National Institute on Drug Abuse, collects data from nonrandom samples of emergency rooms and

Figure 2. Emergency room mentions per million prescriptions, Drug Abuse Warning Network, by year and quarter

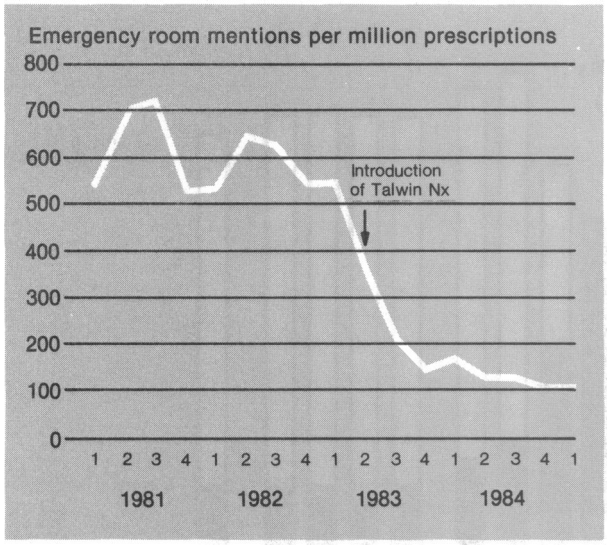
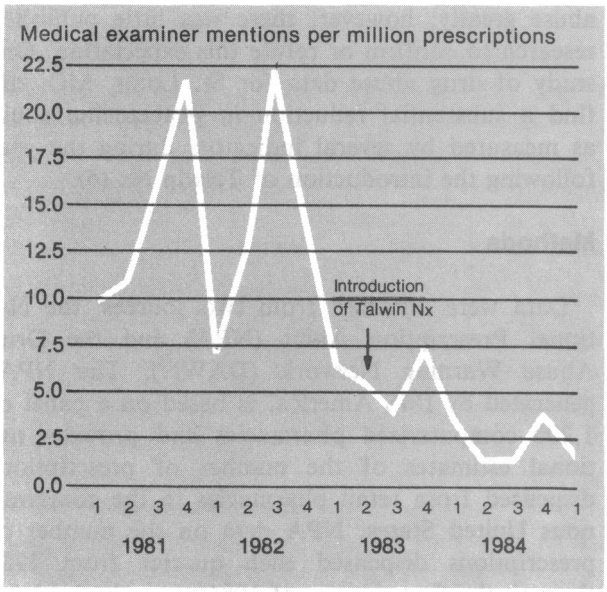


Figure 3. Medical examiner mentions per million prescriptions, Drug Abuse Warning Network, by year and quarter



medical examiners and provides information on drugs "mentioned" in association with a drug abuse episode. Data are not currently extrapolated to the national level. Our analyses were based only on data collected from the same facilities during each period in the study. DAWN provided quarterly data on the number of times pentazocine was mentioned in a DAWN-affiliated emergency room and the number of times pentazocine was mentioned by a participating medical examiner. Both DAWN and the NPA are described more fully elsewhere (*7,8*).

Results

NPA data indicated that the number of prescriptions dispensed for pentazocine products remained fairly constant from the first quarter of 1981 through the first quarter of 1983, but increased after the introduction of Talwin Nx in the second quarter of 1983 (fig. 1). In contrast, the number of DAWN emergency room mentions decreased after Talwin Nx was introduced. Pentazocine was mentioned 4,678 times from 1981 through the first quarter of 1983 ($\bar{x}=520$ emergency room mentions per quarter) and 1,706 times from the second quarter of 1983 through the first quarter of 1985 ($\bar{x}=213$ emergency room mentions per quarter). DAWN also reported a decrease in medical examiner mentions, with a total of 105 medical examiner mentions for pentazocine during the 9 quarters preceding the introduction of Talwin Nx ($\bar{x}=11.7$ per quarter) and 36 mentions during the following 8 quarters ($\bar{x}=4.5$ per quarter.)

The observed decrease in DAWN mentions after the introduction of Talwin Nx is more pronounced if one considers the corresponding increase in the number of prescriptions. From 1981 through the first quarter of 1983, there were 604 emergency room mentions and 14 medical examiner mentions for every million prescriptions dispensed for pentazocine products. Rates for the following 2 years were 180 emergency room mentions and 4 medical examiner mentions per million prescriptions, representing decreases of 70 percent and 71 percent, respectively.

Figures 2 and 3 show quarterly changes in these rates over time. Because both curves appear to have a declining trend, it was necessary to determine whether the decreases in the rates past the second quarter of 1983 could be explained by the overall declining trend or were attributable to other factors. The results of the analysis of covariance showed that neither emergency room nor medical examiner rates shared a common trend before and after introduction of Talwin Nx. These inconsistencies confirmed that the intervention of Talwin Nx was associated with the changes in the trend. We attempted to examine the trends before and after the naloxone intervention; however, for both emergency room and medical examiner rates, the data for the period prior to naloxone intervention were too scattered to produce reliable esti-

mates. After naloxone intervention, the rate of emergency room mentions showed a significant declining trend ($P = .01$), and the change in the rate of medical examiner mentions over time was not statistically significant ($P = .09$) at the .05 level.

Discussion

Despite an increase in the number of prescriptions dispensed for pentazocine products, DAWN emergency room and medical examiner mentions for pentazocine decreased substantially with the substitution of Talwin Nx for oral Talwin. During the 2 years after the substitution, rates for both emergency room and medical examiner mentions were less than one-third of their prior levels. Other factors, such as a possible increase in the availability of heroin, may have contributed to this reduction, but it is unlikely that we would have observed such a dramatic decrease without the naloxone intervention.

Pentazocine abuse has obviously not disappeared entirely, but appears to have leveled off at a much lower and possible endemic rate. It is now less of a concern relative to other drugs. DAWN data for 1984 indicated that pentacozine ranked 42nd among substances mentioned in emergency room drug abuse episodes (as opposed to 16th in 1982), and it was ranked 48th in medical examiner mentions (compared with 33rd in 1982).

Much of the remaining pentazocine abuse appear to be in cases in which the drug was obtained outside of legitimate channels, making it particularly difficult to control by regulatory action. A previous analysis of the 22 prescription drugs most frequently mentioned by emergency rooms in 1983 indicated that pentazocine was obtained by legal prescription in only 21 percent of the episodes in which drug source was known. Only methaqualone had a lower percentage for legal prescriptions, and the 20 other drugs were obtained by legal prescription in a majority of the known-source cases (*8*).

Given the apparent distribution of pentazocine as a street drug and the continuing availability of nonreformulated Talwin in other countries (for example, Canada), further attempts to reduce pentazocine abuse through regulatory measures may have diminishing returns. Pentazocine is still marketed in the United States without concomitant naloxone as an injectable product (Talwin Injection) and in combination with acetaminophen (Talacen) or aspirin (Talwin Compound). The injectable form is not as easily obtainable as oral Talwin was, however, and the inclusion of acetaminophen or aspirin in the combination products makes them less likely candidates for eventual parenteral administration.

'DAWN data for 1984 indicated that pentazocine ranked 42nd among substances mentioned in emergency room drug abuse episodes (as opposed to 16th in 1982), and it was ranked 48th in medical examiner mentions (compared with 33rd in 1982).'

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