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The Diversion of Ultram®, Ultracet®, and Generic Tramadol HCl

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ABSTRACT. Ultram® (tramadol HCl) was approved by the Food and Drug Administration in 1994 as a non-scheduled drug under the Controlled Substance Act. The non-scheduled status was contingent on the development and implementation of a comprehensive postmarketing surveillance program by an Independent Steering Committee external to Ortho-McNeil Pharmaceutical charged with monitoring abuse and recommending scheduling if unexpectedly high abuse occurred. The program developed by this committee was composed of a variety of studies, and the results of the first three years of the surveillance efforts revealed that the rate of Ultram abuse was low. At a meeting of the FDA in 1998 to reexamine the scheduling status of Ultram, it was recommended that the scope of the postmarketing surveillance program be broadened to include data on diversion. After one year pilot study, by January 2002, a nationwide diversion survey was fully operational. This brief communication describes the experiences of this diversion study, and compares the findings on the diversion of Ultram and other tramadol HCl products with that of more widely abused drugs. Survey data suggest that the diversion of Ultram and other tramadol products is low, and overall, diversion investigators did not consider tramadol to be a problem in their respective jurisdictions.

KEYWORDS. Ultram®, Ultracet®, tramadol, diversion

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INTRODUCTION

Ultram® (tramadol HCl), marketed in the United States by Ortho-McNeil Pharmaceutical (OMP), is a centrally acting analgesic with a potency equivalent to low doses of opiates.[1-3] Ultram was approved by the Food and Drug Administration (FDA) in 1994 as a non-scheduled drug under the Controlled Substance Act, based on a recommendation of the FDA's Drug Abuse Advisory Committee (DAAC). The evidence supporting this recommendation was clinical and preclinical data suggesting a low abuse potential, combined with data from the European experience with the drug which reflected a very low rate of abuse. The FDA's decision, however, was contingent on the development and implementation of a comprehensive risk-management program by an Independent Steering Committee external to OMP charged with monitoring abuse. Although the funding for the risk management program was provided by OMP, the Independent Steering Committee nevertheless had the power to recommend scheduling if unexpectedly high abuse occurred. Moreover, the Steering Committee exercised its independence in several other ways: (1) representatives of OMP were not permitted to attend Steering Committee meetings; (2) OMP had no input into the conduct of the studies; (3) all data resided with the investigators; and (4) although OMP had the right to prior review of papers and presentations, their input was in an advisory capacity only.

The program developed by the Independent Steering Committee was composed of a variety of studies, including a survey of a national network of drug abuse experts to detect "signals" that abuse of tramadol might be emerging in their communities, and to estimate rates of abuse as measures of risk/benefit ratios.[4-6] The results of the first three years of these surveillance efforts revealed that, after a period of experimentation, the rate of Ultram abuse declined significantly and stabilized at a low level of 0.5-1.0 case per 100,000 patients prescribed the analgesic.[4] At a meeting of the DAAC in 1998 to reexamine the scheduling status of Ultram, a unanimous decision was made that the risk-management program developed by the Independent Steering Committee did indeed proactively track abuse and that the rates of abuse were even lower than expected in 1994.[7] Although FDA regulatory officials argued that the diversion of Ultram was widespread and represented a potential threat to public health, the DAAC nevertheless recommended that no change be made in scheduling status, but also recommended that the scope of the postmarketing surveillance program be broadened to include data on diversion.[7]

To comply with this request, in 1999 the Independent Steering Committee began examining alternative approaches for monitoring the diversion of Ultram, as well as developing a roster of police agencies throughout the United States that were willing and able to participate in a diversion study. Diversion involves the channeling of prescription medications from legitimate sources to the illegal marketplace. This occurs primarily through: (1) the illegal sale of prescriptions by physicians and pharmacists; (2) "doctor shopping" by individuals who visit multiple physicians to obtain prescriptions; (3) theft, forgery, or alteration of prescriptions by patients; (4) robberies and thefts from pharmacies; and (5) and thefts of institutional drug supplies.

After a 1-year-pilot study, by January 2002, a nationwide diversion survey was fully operational.[8] This brief communication describes the experiences of this diversion study, and compares the findings on the diversion of Ultram and other tramadol HCl products with that of more widely abused drugs.

METHODS

On a quarterly basis, beginning in 2002, 102 drug diversion investigators from police agencies in all 50 states were surveyed regarding: (1) the total number of prescription drug diversion investigations initiated during the last three months; (2) the number of cases investigated involving Ultram; (3) a listing of the top ten drugs diverted and the number of cases of each; and, (4) the street prices of the diverted drugs. Participating investigators (or their agencies) were paid a small stipend for their time and input. The survey is an ongoing effort coordinated by the Independent Steering Committee and supported through an unrestricted research and educational grant from Ortho-

McNeil to Washington University in St. Louis, Missouri.

In October 2001, Ortho-McNeil released a combination product, Ultracet® (325 mg acetaminophen and 37.5 mg tramadol). Moreover, since July of 2002, Ultram has been available as generic tramadol from a number of companies. Both of these products were added to the diversion survey.

RESULTS

During the nine calendar quarters from January 2002 through March 2004, the response rate from the 102 participating agencies averaged 71.2%, and the reporting agencies initiated a total of 16,755 investigations of prescription drug diversion. In the majority of these investigations, more than one drug was mentioned as having been diverted. Notably, hydrocodone was mentioned in 40.1% of the investigations, benzodiazepines (primarily alprazolam and diazepam) in 27.9% of the investigations, oxycodone in 20.2% of the investigations, and tramadol products (Ultram, Ultracet, and generics) in 1.5% of the investigations. The number of mentions in each of these drug categories during each quarter of the survey period is illustrated in Figure 1. The number of hydrocodone mentions was consistently the highest in every quarter, and fairly constant at approximately 800 mentions per quarter. The trend lines for benzodiazepines and oxycodone were similar, and were stable at half the level (i.e., 400 per quarter) of that observed for hydrocodone. By contrast, the number of tramadol diversions was consistently lower over the nine-quarter period, being apparently a tenth the level of the mentions for benzodiazepines and oxycodone.

Figure 2 illustrates the number and percent of mentions of each of the tramadol products over the nine-quarter survey period. The black section at the bottom of the figure corresponds to the percentage of total mentions for Ultram, the top section in gray corresponds to generic tramadol, and the middle section in white corresponds to Ultracet. The top of the figure contains the actual number of mentions for each drug in each calendar quarter. Overall, the diversion of tramadol products began at a peak of 42 mentions during the first quarter of 2002 in the jurisdictions being monitored, followed by a stable level around 30 cases per quarter. The

FIGURE 1. Total Diversion Mentions for Hydrocodone, Benzodiazepines, Oxycodone, and Tramadol HCl for 2002, 2003, and First Quarter 2004

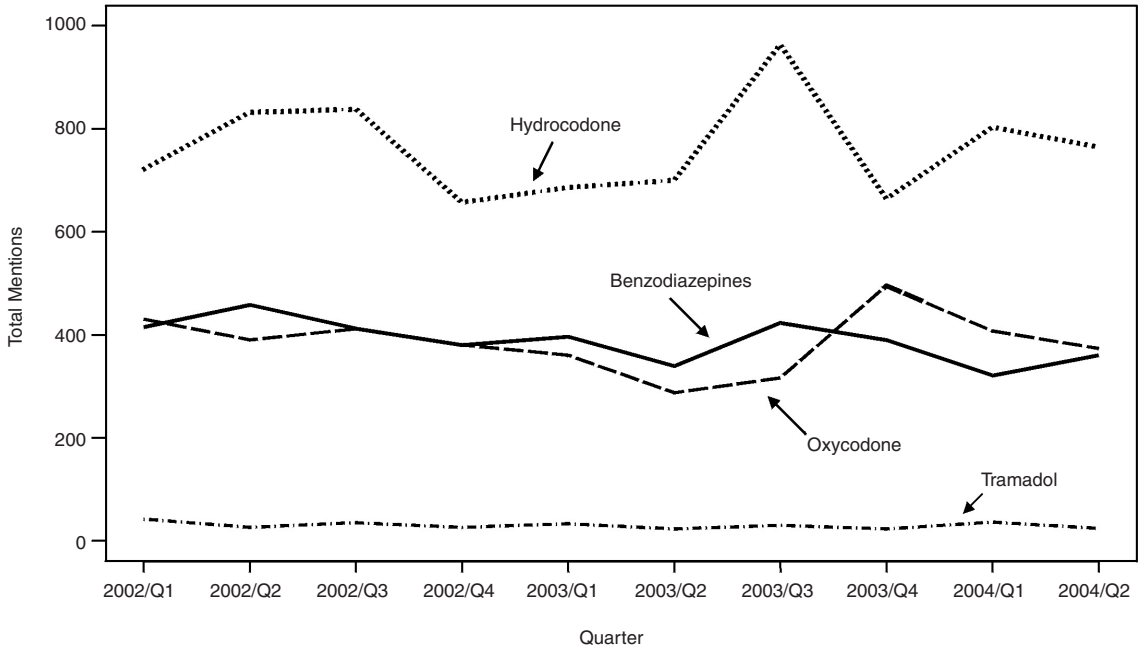
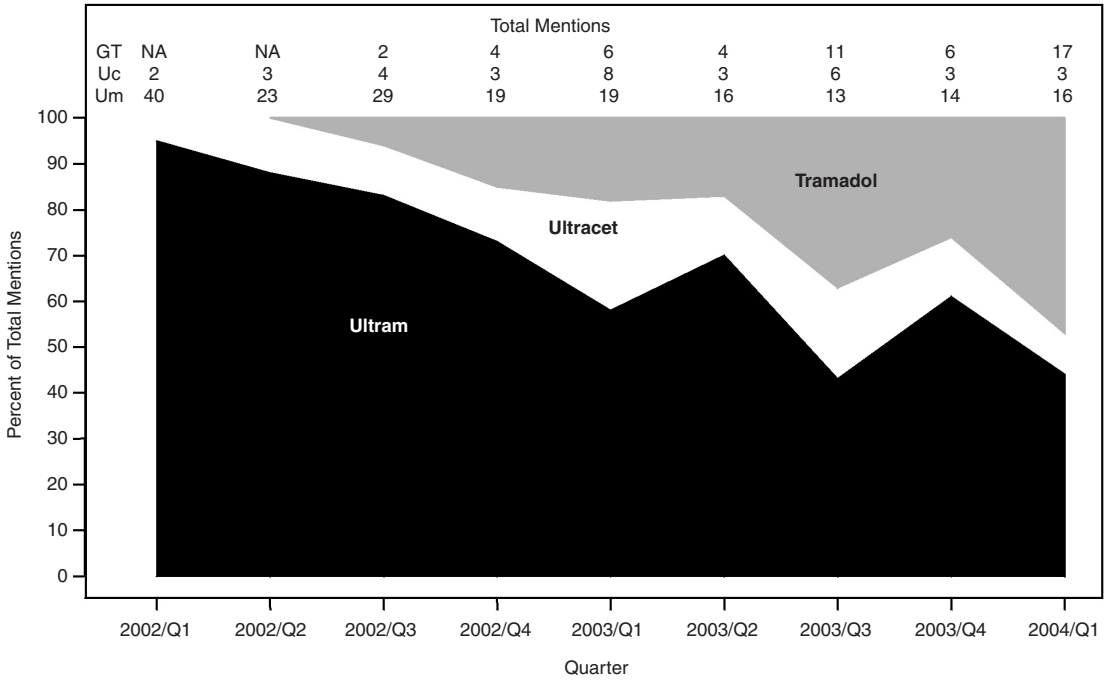


FIGURE 2. Proportion of Diversion Mentions Involving Ultram (Um), Ultracet (Uc), and Tramadol (GT) for 2002, 2003, and First Quarter 2004



bulk of these diversions were for Ultram–declining from 95.2 percent in the first quarter of 2002 to 44.4 percent in the first quarter of 2004. There were corresponding increases in the diversion of the other tramadol products as they were introduced. Notably, the diversion of Ultram and generic tramadol was equal in the first quarter of 2004. The diversion of Ultracet was a relatively rare event throughout the survey period. The street prices for all of the tramadol products were typically at, or below, the pharmacy prices, and significantly less than internet pharmacy prices, suggesting a limited interest in these drugs on the illicit market. Overall, diversion investigators did not consider tramadol to be a problem in their respective jurisdictions.

DISCUSSION

The abuse of opioid pain relievers has been recognized as a serious and growing public health problem. Recent estimates from the Drug Abuse Warning Network, for example, indicate that drug abuse-related emergency department visits involving opioid pain relievers have been increasing steadily, from 45,254 in 1995 to 119,185 in 2002.[9] Moreover, these drugs accounted for 10 percent of all drug mentions in drug abuse-related emergency department visits in 2002. Similarly, data from the Treatment Episode Data Set (TEDS) indicate that drug abuse treatment admission rates involving opioid pain relievers reflect a 155% increase over an 11-year period, from 14 per 100,000 persons (ages 12 and up) in 1992 to 35 per 100,000 population by 2002.[10] Finally, the number of persons ages 12 and older reporting lifetime nonmedical use of opioid pain relievers in the National Survey of Drug Use and Health (NSDUH) increased from 29.6 million in 2002 to 31.2 million in 2003.[11,12] In all three reporting systems, the opioids most frequently mentioned were hydrocodone and oxycodone. In the NSDUH data specifically, hydrocodone was the most often abused of the opioids, involving 17.7 and 21.4 million individuals in 2002 and 2003, respectively, followed by oxycodone, with 11.6 and 13.6 million persons in 2002 and 2003, respectively. By contrast, the numbers reporting lifetime nonmedical use of

tramadol in 2002 and 2003 were 52,000 and 186,000, respectively. Because of their high abuse potential, oxycodone is designated as a Schedule II drug and hydrocodone as a Schedule III drug under the Controlled Substances Act. Yet despite the non-controlled status of tramadol, the diversion of Ultram, Ultracet, and generic tramadol would appear to be minimal. Moreover, the relative rankings of hydrocodone, oxycodone, and tramadol in the NSDUH data correspond to diversion data described here.

Although this report suggests that the diversion of tramadol is very limited in comparison to other opioid pain relievers, the data in this report suffer from a number of limitations. First, of the more than 23,000 police departments and other law enforcement agencies in the United States, it is likely that less than 10 percent have officers assigned to prescription drug diversion. In fact, even among the thousands of municipal, county, and state police agencies that place a significant emphasis on drug enforcement, few target prescription drugs. Federal agencies, and particularly the Drug Enforcement Administration (DEA), have declined to participate in the survey. In fact, as a matter of policy, neither the FDA nor the DEA participate in industry-sponsored studies. Given the limited number of agencies willing and able to participate in the survey, the levels of diversion of hydrocodone, oxycodone, tramadol, and all other drugs monitored in the survey are significantly under reported. Second, a few police agencies that agreed to participate in the survey do not necessarily respond every quarter, and some have never responded. The problem is that the focus of police activity is often a political decision. If additional police personnel are needed at any given time to respond to a particular crisis or perceived crisis–such as prostitution, crack sales, anti-terrorism efforts, a highly visible violent or property crime, or whatever–resources are shifted to these areas. The less visible criminal activities, such as prescription drug diversion, tend to take a back seat-sometimes temporarily, sometimes permanently. And finally, from quarter to quarter, there are a few "dropouts" from the survey, who withdraw from the survey for a variety of reasons-limited time or police resources to devote to the survey, reassignment of officers in the diversion unit to other tasks, or implementing of new policies, which prohibit police participation in the survey. Although these individuals are replaced, the sample participants change from time to time. Nevertheless, the nationwide distribution of agencies would appear to be sensitive, and capable of detecting the diversion of tramadol, which has been demonstrated in studies of other drugs, which have a low abuse potential.

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