

ORIGINAL REPORT

# Rates of abuse of tramadol remain unchanged with the introduction of new branded and generic products: results of an abuse monitoring system, 1994–2004

Theodore J. Cicero PhD<sup>1\*</sup>, James A. Inciardi PhD<sup>2</sup>, Edgar H. Adams ScD<sup>3</sup>, Anne Geller MD<sup>4</sup>, Edward C. Senay MD<sup>5</sup>, George E. Woody MD<sup>6</sup> and Alvaro Muñoz PhD<sup>7</sup>

<sup>1</sup>Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO, USA

<sup>2</sup>University of Delaware, Coral Gables, Delaware, FL, USA

<sup>3</sup>Harris Interactive, 5 Independence Way, Princeton, NJ, USA

<sup>4</sup>St. Luke's/Roosevelt Hospital Center and Columbia University College of Physicians & Surgeons, New York, NY, USA

<sup>5</sup>Pritzker School of Medicine, University of Chicago, Chicago, IL, USA

<sup>6</sup>University of Pennsylvania, Philadelphia, PA, USA

<sup>7</sup>The Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA

## SUMMARY

**Purpose** The analgesic Tramadol HCl (Ultram<sup>TM</sup>) was approved in 1994 as a non-scheduled drug under the CSA provided that a novel risk-management program would be developed by an Independent Steering Committee (ISC). The risk-management program began in 1995 with the launch of Ultram, and has been modified over the past decade to accommodate Ultracet (Ultram and acetaminophen) in 2001 and generic tramadol in 2002. This provided a unique opportunity to study the potential changes in abuse as the generic and combination products became available.

**Methods** To proactively detect cases of abuse and diversion, the ISC developed a comprehensive questionnaire which was completed quarterly by an extensive network of drug abuse experts ( $n = 309$ ) and police agencies ( $n = 100$ ) who were asked to indicate how many diversion cases involving Ultram, Ultracet, and generic tramadol were identified during the preceding 3 months and what were the ten most commonly diverted drugs in their catchment area during that period.

**Results and Conclusions** The data generated demonstrate that the abuse of tramadol remained very low despite new branded and generic formulations. Contrary to the hypothesis that cheaper generic drugs would lead to higher rates of abuse, we found no increase in abuse with the introduction of generic tramadol. Ultracet abuse rates, unlike those found with other widely used hydrocodone and oxycodone combination products, have been even lower than that observed for tramadol. Since the FDA has now mandated that proactive risk-management plans be implemented for new drugs, the tramadol risk-management plan may be useful as a prototypic model which can be modified to accommodate other drugs with abuse potential. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — risk-management; post-marketing surveillance; Ultram; tramadol; Ultracet; drug abuse; drug diversion

## INTRODUCTION

Tramadol HCl is a centrally active analgesic with affinity for  $\mu$ -opioid receptors.<sup>1–6</sup> It was marketed as Ultram<sup>®</sup> (hereafter referred to as branded tramadol) by Ortho-McNeil Pharmaceutical (OMP) in the U.S.A. beginning in 1995 as a non-scheduled drug, based on pre-clinical,<sup>7–10</sup> clinical,<sup>11–14</sup> and epidemiological data gathered in Europe<sup>15</sup> suggesting a low

\* Correspondence to: Dr T. J. Cicero, Department of Psychiatry, Washington University, Campus Box 8027, 660 S. Euclid Avenue, St. Louis, MO 63110, USA. E-mail: cicerot@wustl.edu

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abuse potential. However, because of fears that the passive surveillance systems used by the FDA<sup>16,17</sup> might not detect abuse in a timely fashion, OMP and the FDA endorsed a proposal that a risk-management program would be established, and overseen by an independent steering committee (ISC), that would monitor abuse of branded tramadol in 'real time.'

The program developed by the ISC and the results of the first years of surveillance has been described previously.<sup>18–20</sup> Briefly, after a brief period of experimentation, the rate of branded tramadol abuse stabilized at a low level of 0.5–1.0 case per 100 000 patients prescribed the analgesic. As the branded tramadol risk-management program evolved from 1995 to 2003, two important modifications were made. First, the program was enhanced to accommodate the introduction of Ultracet (branded tramadol/acetaminophen) in October 2001 and generic tramadol in July 2002; and, second, a complementary program to monitor the illicit diversion of tramadol was initiated in 2002.

The introduction of generic tramadol, at greatly reduced price, provided a unique opportunity to assess the relationship between the price of prescription drugs and their abuse liability. Many studies have shown a negative correlation between the price of licit (alcohol, nicotine) and illicit drugs (cocaine, marijuana, and heroin) and the magnitude of their abuse,<sup>21–24</sup> but there are no such reports examining this relationship with prescription drugs. Thus, apparently for the first time, the ISC was able to test the hypothesis that a steep reduction in the price of a prescription drug would increase its rate of abuse. In addition, the introduction of branded tramadol/acetaminophen was expected to increase total market penetration of tramadol products since it carried an indication for acute pain, whereas tramadol was indicated for chronic pain. Thus, the ISC postulated that this increased exposure would lead to proportionally greater abuse rates, much as has been observed with hydrocodone and oxycodone combination products.<sup>25–27</sup>

## METHODS

### *General methodological issues*

All of the prescription data for generics were purchased by OMP through IMS (IMS Health, Inc.) which enabled the ISC to calculate a total denominator of patients exposed to branded and generic tramadol and branded tramadol/acetaminophen. The ISC also obtained the agreement of the three largest of 11 generic companies, which collectively sold over

80% of all the generic tramadol, to provide spontaneous reports of abuse they received.

### *Identifying cases of abuse of branded tramadol, generic tramadol, and tramadol/acetaminophen*

*Key informant network.* Data were collected quarterly from a network of so-called 'key informants'<sup>18</sup> that consisted of 110 National Institute on Drug Abuse grantees and 145 other drug abuse experts, who were in a position to know about new and emerging drug problems in their areas. Additional information was collected in positive cases of abuse and withdrawal from interviews, reviews of patient charts and, in some cases, interviews by individual members of the ISC.<sup>18–20</sup>

*Diversion.* The participating sites were recruited through traditional chain referral/snowball sampling strategies. The ISC began with an established network of drug diversion investigators; all investigators were asked for leads to other agencies that might be contacted. Participating agencies ( $n = 100$ ) were asked to indicate how many diversion cases involving branded tramadol, tramadol/acetaminophen, and generic tramadol were identified during the preceding 3 months and what were the ten most commonly diverted drugs in their catchment area during that period.

### *Evaluation of reports of abuse*

As described elsewhere,<sup>18–20</sup> all spontaneous reports of abuse of branded tramadol, generic tramadol, and of branded tramadol/acetaminophen obtained from OMP, the generic companies and the proactively elicited cases from the ISC, were evaluated and classified by a sub-committee of the ISC according to Diagnosis and Statistical Manual, 4th Edition (DSM-IV) criteria for substance abuse and dependence and withdrawal.<sup>18–20,28</sup>

All of the reports evaluated by the ISC were transmitted to OMP and the generic companies, which in turn were submitted to the FDA under the MedWatch system. The diversion cases were not clinically evaluated since the ISC assumed that arrests for illegal diversion of tramadol were by definition abuse.

### *Estimation of patient exposure and rates of abuse*

Rates of abuse (cases/100 000 patients prescribed tramadol) for all key informant cases were calculated to correct for the degree of exposure. For diversion, mentions of drug seizures are simply presented as the raw number of cases, not rates, because it is impossible to calculate a rate. Specifically, diversions

involve forged, altered, or illegally obtained prescriptions, or possession of very small quantities of the drugs. For this reason, rates based on 'tablets in patients' hands' would be inappropriate and might tend to minimize the actual magnitude of the problem.

Cicero *et al.*<sup>18</sup> described the methods to estimate the number of individuals exposed to branded tramadol on the basis of tablets sold and in patient's hands (i.e., including those in inventory) and key descriptors of prescription practices (e.g., size of the prescription). To estimate the number of individuals exposed to generic tramadol, we used the data on tablets sold in a given month and assumed that the ratio of tablets sold to the number of individuals exposed were the same for branded tramadol and generic tramadol. By July 2003, the number of individuals exposed to branded tramadol reached very low levels making the estimation unreliable and, thus, we used July 2003 as the final date of analyses for branded tramadol and generic tramadol. Data for the branded tramadol/acetaminophen product and diversion of all tramadol products were still available after 30 June 2003 and we present here data up to December 2003.

#### *Statistical methods*

To determine the trends of the rates of abuse and to test whether the rate of abuse of branded and generic tramadol was the same as that of the branded tramadol/acetaminophen product, we used regression methods based on the number of abuse reports following a Poisson distribution whose mean (and variance) was the product of the number of individuals exposed and the rate of abuse.<sup>18</sup>

#### *Patient/subject confidentiality*

This protocol has been approved by the Washington University Institutional Review Board.

## RESULTS

#### *Catchment areas of the key informant and diversion networks*

Figure 1 shows the distribution of key informants and diversion investigators by their three-digit ZIP code mailing address. As can be seen, much of urban and rural America is covered by one, two or both of the networks. Most often, the catchment areas of the key informants and diversion experts was four to five three-digit ZIP codes, including their own mailing ZIP code.

#### *Estimated patient use of tramadol and generic tramadol*

The monthly estimates of the total number of patients prescribed branded or generic tramadol and the branded tramadol/acetaminophen product are shown in Figure 2. The number of patients prescribed tramadol reached an asymptote of more than one million patients per month from 1999 to 2002. The introduction of generic tramadol in 2002 abruptly reduced (>85%) the number of people prescribed branded tramadol, and by the second quarter of 2003, it represented only 7% of total tramadol sales. The branded tramadol/acetaminophen product was introduced in July 2001 and its use steadily increased to over half a million patients per month by 31 December 2003.

#### *Rates of abuse of branded and generic tramadol and tramadol/acetaminophen*

Figure 3 shows the rates of abuse of branded tramadol, generic tramadol, and the combination product. There was no effect of generic tramadol on abuse rates. In addition, the average rate of abuse for branded tramadol/acetaminophen was approximately 0.25 cases per 100 000 individuals exposed in the 2 years it was available and was significantly lower (<0.001) than that observed with tramadol. The introduction of generic tramadol had no effect on the rates of withdrawal (Figure 4). In the case of branded tramadol/acetaminophen, there was an abrupt surge in withdrawal reports to 1.2 cases/100 000 the second quarter after its launch, but thereafter the rates dropped to 0–0.5 cases/100 000.

#### *Characterization of abuse*

The histories of drug/alcohol abuse were available in approximately two-thirds of all abuse/dependence cases of branded or generic tramadol and tramadol/acetaminophen. In approximately 96% of the tramadol and 94% of the tramadol/acetaminophen cases, there was a history of opiate, alcohol, or other drug abuse.

#### *Diversion*

During calendar years 2002 and 2003, the diversion reporting sites initiated a total of 7483 investigations of pharmaceutical diversion, the vast majority of which were for pain medications. The most widely diverted opiate drugs were hydrocodone with 690



Figure 1. Distribution of key informants and diversion investigators by their three-digit zip code mailing addresses

mentions per quarter and oxycodone with 370 mentions per quarter. Tramadol products were diverted much less frequently, at a rate of  $\cong 30$  mentions per quarter. Stated differently, of the 7483 cases of diversion, opiate analgesics were involved in 75% of these cases, whereas tramadol in all of its formulations was indicated in less than 0.05%.

#### *Geographical stratification of abuse and diversion*

Informants and diversion specialists in 28 and 48 zip codes, respectively, never observed any abuse or diversion of branded or generic tramadol and tramadol/acetaminophen in nearly a decade covered by this surveillance effort. Of those zip codes in which cases of abuse or diversion were found, they were confined largely to relatively small cities and rural areas with very little persistent abuse or diversion observed in the nation's largest cities with substantial heroin and

other opiate abuse problems as reported previously.<sup>18–20</sup> The abuse and diversion of branded tramadol and generic tramadol was also transient in nature. The maximum number of times any abuse of branded and/or generic tramadol was found in a specific zip code ranged from 6 to 13 of 37 possible quarters. In the case of diversion, only one zip code (Jackson, MS) reported abuse in all eight possible quarters; all of the other zip codes reported less frequent occurrences of diversion.

#### DISCUSSION

A unique aspect of this pharmacovigilance program set up in 1995 to monitor the potential abuse of tramadol was that the ISC was able to track abuse of a newly marketed drug (branded tramadol) from the date of its launch through the introduction of generics, and the launch of the combination product tramadol/

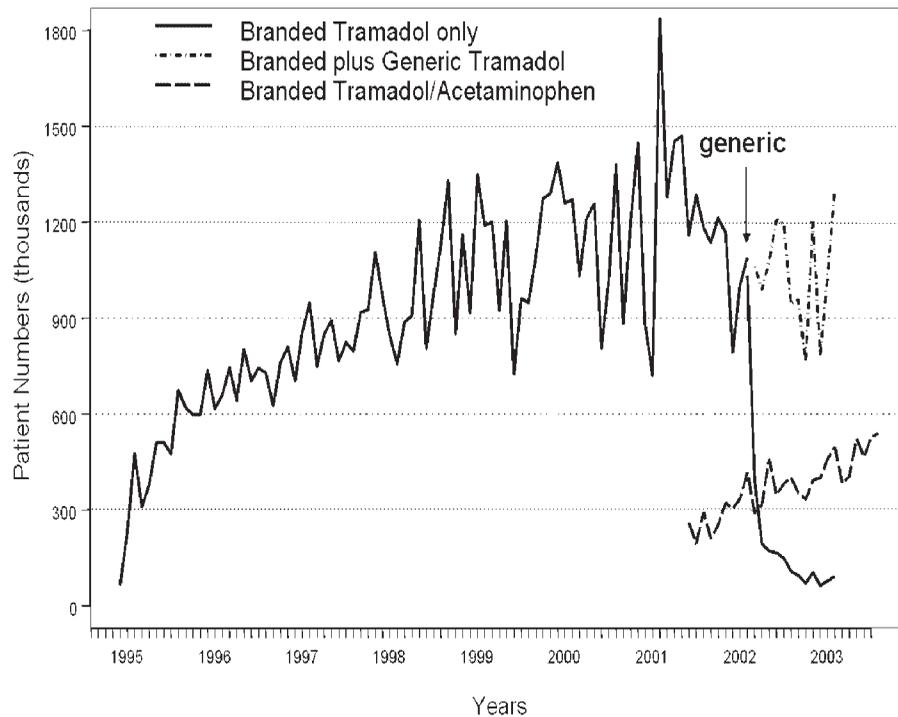


Figure 2. The total number of patients in thousands exposed per month in the United States from 1 May 1995 to 30 June 2003 for branded and generic tramadol and to 31 December 2003 for branded tramadol/acetaminophen. The data from 1995 to 1998 have been reproduced from a prior publication<sup>18</sup>

acetaminophen. Thus, the ISC was able to test the hypothesis for the first time that the cost of prescription drugs may be inversely related to their abuse much as has been observed with both licit (i.e., alcohol and nicotine) and illicit drugs of abuse.<sup>21–24</sup> Our results described in this article indicate that the cost of the drug seems to be irrelevant with regard to its abuse. The introduction of generics, which on average were 30–40% cheaper (\$0.64–\$0.73) than branded tramadol (\$1.25), did not increase rates of abuse at all. Whether this lack of a relationship between price and abuse holds true for other more abusable prescription drugs needs to be evaluated.

The launch of the tramadol/acetaminophen product, with an indication for acute pain, was expected to markedly increase the total population exposed to tramadol products, which is precisely what we observed (Figure 2). With that enhanced exposure, more abuse was anticipated much as has been observed with hydrocodone and oxycodone preparations. We found no support for this supposition. The most common adverse event detected for tramadol/aceta-

minophen was withdrawal, which rose to more than 1 case/100 000 the second quarter after its launch, but thereafter dropped to less than 0.5 cases/100 000. This abrupt increase in withdrawal soon after its introduction apparently resulted from many physicians suddenly shifting from branded or generic tramadol (50 mg per tablet) to the lower dose tramadol/acetaminophen product (37.5 mg) which may have elicited mild withdrawal in the opiate-tolerant pain patient. The withdrawal observed with tramadol/acetaminophen was generally typical opioid withdrawal with very small numbers of atypical withdrawal cases.<sup>19</sup>

As previously described, the abuse of tramadol and tramadol/acetaminophen was found almost exclusively (>95%) in individuals with a past history of substance abuse. These observations are consistent with prior reports that the therapeutic use of drugs rarely leads to abuse in pain patients,<sup>29–31</sup> although fears of drug addiction remain a major concern of physicians that inappropriately limits the use of analgesics.<sup>32,33</sup>

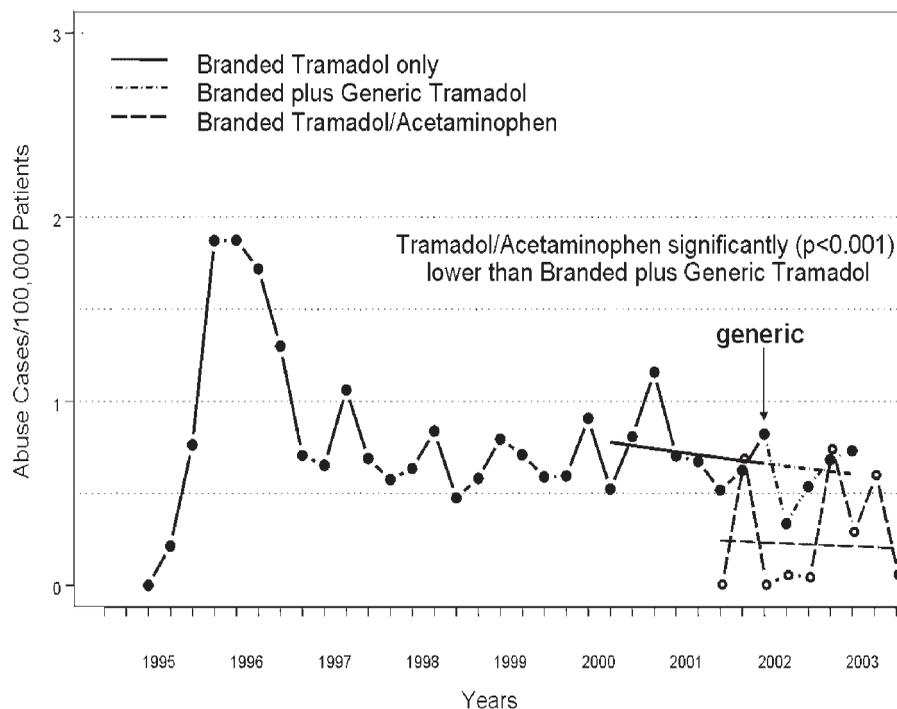


Figure 3. Rates of abuse/dependence of branded and generic tramadol and branded tramadol/acetaminophen from May 1995 to 30 June 2003 (tramadol) and to 31 December 2003 (branded tramadol/acetaminophen). Using Poisson regression methods, the best fit line describing the rate of branded tramadol/acetaminophen abuse from October 2001 to December 2003 was significantly ( $p < 0.001$ ) lower than the line describing the rates of abuse of tramadol in the 2 years ending June 2003 when branded tramadol sales declined to  $< 10\%$  of market. The distance between the two regression lines using Poisson regression methods was significant ( $p = 0.007$ ) in the direction of branded tramadol/acetaminophen abuse rates being lower than that observed with tramadol. The data from 1995 to 1998 have been reproduced from a prior publication<sup>18</sup>

The most striking feature of the branded and generic tramadol and tramadol/acetaminophen abuse and diversion data were that they were confined to the suburbs of large cities, small urban centers, and rural areas, which in some cases had a long history of abuse of prescription medications.<sup>25,26,34–37</sup> Very few cases were detected in the largest cities in the country where heroin abuse is endemic. Our initial hypothesis was that the introduction of cheaper generics and combination products for acute pain might enhance the acceptance and abuse of tramadol in inner cities where cost may be a factor in prescription drug abuse. This clearly did not occur. From informant responses, there may be a number of reasons for this: first, tramadol is rarely used when more potent and attractive euphorigenic opiates are readily available; second, the use of prescription drugs is more socially acceptable than heroin or cocaine in non-urban, more affluent areas; and, finally, the purity and dosage of prescription

medications are highly predictable, suggesting that they are much safer to use than illicit drugs.

The ISC recognizes that this risk-management program suffers limitations, the most significant of which is the somewhat anecdotal nature of the information provided by our key informants and diversion investigators, which leads to some uncertainty about the actual number of cases or rate of abuse and withdrawal of branded, generic tramadol, and tramadol/acetaminophen. This defect is further exacerbated in the diversion studies in which tramadol diversion may be underestimated because it is a non-scheduled drug, the possession of which may not lead to an arrest in some jurisdictions.

Thus, the true rates of abuse and diversion may be somewhat imprecisely estimated. However, it is important to note that this imprecision is equiponderant with respect to the estimation of abuse and diversion rates of branded tramadol, generic tramadol,

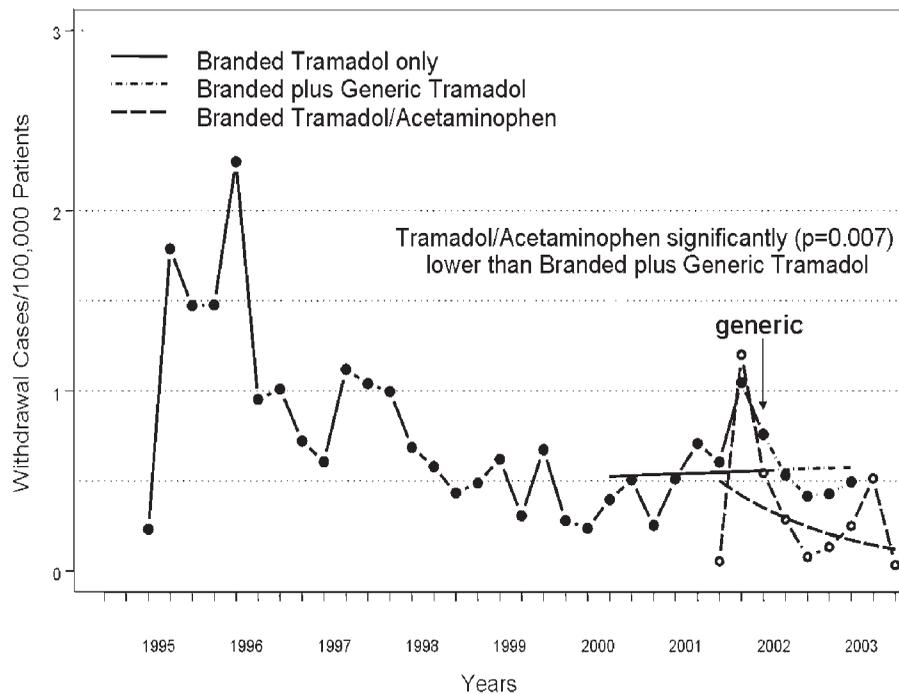


Figure 4. Rates of withdrawal from branded and generic tramadol and branded tramadol/acetaminophen from May 1995 to 30 June 2003 (tramadol) and to 31 December 2003 (branded tramadol/acetaminophen). Using Poisson regression methods, the best fit line describing the rate of branded tramadol/acetaminophen withdrawal from October 2001 to December 2003 was significantly ( $p \leq 0.007$ ) lower than the line describing the rates of tramadol withdrawal in the 2 years ending June 2003 when branded tramadol sales declined to <10% of market. The data from 1995 to 1998 have been reproduced from a prior publication<sup>18</sup>

and tramadol/acetaminophen. Therefore, the results are all biased to the same extent leading to precisely the same results and conclusions. Nevertheless, we believe the proper interpretation of these types of surveillance efforts is that they provide a 'signal' that abuse may be occurring in a specific region which warrants more detailed analysis. With a proper scientific study of the root causes of abuse in these areas, it should be possible to develop intervention strategies to reduce abuse (i.e., risk-management) as was done in the early stages of this decade old program.<sup>18</sup>

The careful monitoring of abuse described in this article did not detect any increase in abuse during the rapid transition to generic tramadol and the introduction of tramadol/acetaminophen. This supports the continuation of the status of tramadol as an unscheduled drug. Moreover, since the FDA now requires risk-management programs but has not provided any formal guidelines about the development of these programs, the ISC suggests that the program described in this article can serve as a prototype, which can be modified to accommodate other drugs with abuse potential.

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#### KEY POINTS

- Abuse of Ultram, tramadol, and Ultracet are very low.
- Generic, cheaper drugs do not necessarily increase use or abuse.
- Risk-management programs that meet FDA expectations can be effectively implemented.
- Prescription drug abuse is prevalent in rural areas and small urban regions.
- Prescription opiate abuse is rarely seen in large cities with substantial heroin problems.

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