ORIGINAL REPORT

Relationship between therapeutic use and abuse of opioid analgesics in rural, suburban, and urban locations in the United States[†]

Theodore J. Cicero PhD[1]*, Hilary Surratt PhD[2],
James A. Inciardi PhD[2] and Alvaro Munoz PhD[3]

[1]*Washington University School of Medicine, MO, USA*
[2]*University of Delaware, Coral Gables, FL, USA*
[3]*Johns Hopkins School of Public Health, Baltimore, MD, USA*

SUMMARY

Purpose   The goal of these studies was to determine the relationship between prescribed use of opioid analgesics and their non-medically related use (abuse) at a regional level across the country.
Methods   To gather information about prescription drug abuse, we asked 233 drug abuse treatment specialists to provide us Quarterly reports on the number of cases of prescription opioid analgesic abusers who used opioid analgesics to get high in the past 30 days.
Results and Conclusions   We found that there was a very strong correlation between therapeutic exposure to opioid analgesics, as measured by prescriptions filled, and their abuse. There were, however, geographical loci that represented outliers in which abuse was disproportionately high relative to therapeutic use (>95th percentile), most of which were in very small urban, suburban, and rural areas. The rank order of abuse shows that buprenorphine products, extended release (ER) oxycodone and methadone are the most intensely abused prescription opioid analgesics, with hydrocodone the least abused, when the data are corrected for degree of exposure, i.e., cases/1000 persons filling a prescription. If, on the other hand, one uses the number of cases/100 000 population, hydrocodone ranked as high as ER oxycodone and all other drugs grouped together at very low levels of abuse. Since the latter conclusion ignores therapeutic exposure, we conclude that the rate of abuse of highly efficacious opioid analgesics is best expressed as cases of abuse/1000 persons filling a prescription, which yields the best possible estimate of the risk-benefit ratio of these drugs. Copyright © 2007 John Wiley & Sons, Ltd.

INTRODUCTION

There has been a surge in abuse of prescription opioid analgesics, over the past decade.[1–6] In the present studies, we sought to address a fundamentally important assumption made implicitly by federal regulatory agencies and in the drug abuse literature[7] that to our knowledge has never been addressed with any scientific data: that the abuse of opioid analgesics

*Correspondence to: Dr T. J. Cicero, Department of Psychiatry, Washington University, Campus Box 8134, 660 S. Euclid Avenue, St. Louis, MO 63110, USA. E-mail: Cicerot@wustl.edu
[†]No conflict of interest was declared.

in a specific community is directly proportional to the therapeutic use of that drug. This assumption has important implications for the medical use of these drugs, particularly with respect to the estimation of a risk-benefit ratio which forms the basis for the medically appropriate use of any class of drugs, all of which have adverse events.

In this connection, it is important to stress that the *rate* at which an adverse event occurs as a function of legitimate therapeutic use of the drug is the most appropriate measure of a risk-benefit assessment, rather than the number of adverse events alone. This rate has traditionally been expressed as the number of adverse events divided by the number of people benefiting from the therapeutic use of the drug. Thus, if one reads the Physician's Desk Reference,[8] for example, rates of occurrence of adverse events are listed as the percentage of people who experience an adverse event while using the drugs therapeutically at the doses recommended.

The problem with abuse as an adverse event, and hence, the calculation of a rate, is that abuse is not generally associated with therapeutic use of opioid analgesics. Rather, diversion to an unintended population (e.g., recreational or street drug abusers) is the most frequent pattern of abuse. Hence, the only accurate rate would be the total abuse cases divided by all of those exposed to the drugs, either as patients or those who have obtained the drug illicitly (e.g., forged prescriptions, theft, drug dealers, etc.). Obviously, this denominator is elusive and will never be estimated with any certainty. It is necessary, therefore, to resort to the use of proxy measures to estimate exposure and, thereby, calculate rates. From the perspective of risk-benefit ratios we argue that the most meaningful proxy is the number of individuals who use the drug therapeutically. Thus, a rate defined as the number of cases of abuse (i.e., the risk) divided by the number of people who are prescribed the drug (the benefit) represents the most informative expression of the incidence of abuse. In this paper, we calculated the rates of abuse for the 8 most commonly used and abused opioid analgesics in 165 of the nation's 997 three-digit postal ZIP codes, for which we had accurate estimates of both therapeutic use (i.e., persons filling a prescription) and abuse.

METHODS

Recruitment of subjects

To gather information about prescription drug abuse we employed a key informant network, consisting of 233 drug treatment centers, located in 165 of the nation's 997 three-digit ZIP codes, representing urban, suburban, and rural locations. This informant network, which is fully described in earlier studies,[2,3] was composed of a large group of treatment center directors specializing in adult and adolescent addiction treatment. In a quarterly questionnaire, we requested that treatment centers provide us with the number of individuals who: first, had a diagnosis of prescription drug abuse, using Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, (DSM-IV)[9] criteria for abuse; and, second, used an opioid analgesic to get high in the past 30 days. The drugs for which we asked information were: hydrocodone, hydromorphone, morphine, fentanyl, methadone, extended release (ER) oxycodone, immediate release (IR) oxycodone formulations, and buprenorphine. In this paper we have pooled branded and generic ER oxycodone and fentanyl products which became available in the second quarter of 2004 and the first quarter of 2005, respectively. The date of the introduction of the generics is indicated by an arrow in all figures. When two or more treatment centers were located in the same ZIP code, the average number of cases per ZIP code was used to define the numerator. To validate that the number of cases provided by the treatment centers was reasonably accurate and that the cases satisfied DSM-IV criteria for abuse, we randomly selected a third of the treatment specialists ($N = 87$) to recruit as many patients as possible from the 1st quarter of 2005 to the 3rd quarter of 2006, with a diagnosis of prescription opioid analgesic abuse to complete a detailed questionnaire. Slightly more than 40% of the entire population of patients agreed to answer the questionnaire and returned it directly to this site (i.e., the treatment directors did not have access to the questionnaires). The questionnaire assessed the degree to which the subjects met DSM-IV criteria for abuse or dependence, demographic issues, where they obtained their drugs, and their drug usage patterns, particularly their use of drugs to get high in the past 30 days. We found an excellent correspondence ($\pm10\%$) between the number of cases estimated by the treatment specialists and the number of completed questionnaires filled out by their clients. Over 91% of the clients satisfied DSM IV criteria for abuse as had been indicated by the treatment directors. Thus, based on this very large sample, we assumed that all 233 treatment center directors provided us valid numbers of abuse cases which satisfied DSM-IV criteria for abuse.

Denominator based on individuals exposed to drugs of interest to calculate rates

The total number of individuals who use a drug is determined from the recipients of a dispensed drug who were prescribed the drug by a physician for therapeutic use (N) and those who used the drug but for whom the drug was not prescribed (m), but rather was obtained illicitly. The drugs used illicitly by the m individuals could come from the drug dispensed to the N individuals (i.e., individuals for whom the drug was dispensed shared drug with other individuals) or come directly from pharmacists or manufacturing sources (e.g., by robberies). There are also individuals for whom the drug is legitimately dispensed, but who did not use any of the drug dispensed to them (n). Thus, the total users are defined as $m + N - n = N + (m - n)$. It is important to note that N may in fact be accurate because it depends on the balance between the number of illicit users and the number of individuals for whom the drug is prescribed but not used and discarded or permanently stored. Neither m nor n is available and, thus, the only denominator known with certainty is the number of individuals for whom the drug is prescribed (N). We purchased this information for each three-digit postal ZIP code from Verispan, Inc. (Yardley, Pennsylvania). We have designated these individuals as Unique Recipients of Dispensed Drugs (URDDs), since this database does not count individuals more than once in a specific quarterly reporting point. We used URDDs as a measure of therapeutic use and as the denominator to calculate rates of abuse at the three-digit ZIP code level for each drug in each quarter (i.e., informant reported number of abuse cases divided by URDDs). To identify three-digit ZIP codes and drugs with disproportionately high rates of abuse, we developed a graphical display for the rates of abuse of each drug in all three-digit ZIP codes in a specific quarter. The ZIP codes and drugs lying above the 95th percentile of the rates for all ZIP codes and drugs in a given quarter provided the means to identify geographical loci and drugs with disproportionately high abuse.

To determine the extent by which an increasing therapeutic exposure increases the number of cases of abuse, we used a logistic regression with the odds ratio of cases being above 5 as the outcome and the URDDs in the log10 scale as the independent variable. The antilog of the regression coefficient of the independent variable represented the odds ratio of cases being more than 5 for each 10-fold increase in the URDDs. The units of analysis were the three-digit ZIP codes/quarters for the calendar year from the 2nd quarter of 2005 to the 1st quarter of 2006 and a separate analysis was carried out for each of the eight drugs of interest.

Denominator based on population

Since regulatory agencies—the Food and Drug Administration and Drug Enforcement Administration—often focus exclusively on sheer numbers of abuse cases, we also calculated rates as average number of cases of abuse/1 million people in each of the three-digit ZIP codes we monitored. Our rationale for standardizing abuse rates in this manner was to correct for large population differences and yield rates which were comparable across all ZIP codes. In addition, we reasoned that five cases of abuse, for example, in a city of 1 million might be considered insignificant whereas in a town of 15 000 it might be of grave concern.

Patient/subject confidentiality

The questionnaire that was transmitted to Washington University did not elicit any individual information (i.e., it was de-identified). The protocol was approved by the Washington University Institutional Review Board (IRB).

RESULTS

Location of treatment centers

The distribution of treatment directors by three-digit postal ZIP code is shown in Figure 1. There are 997 three-digit ZIP codes in the continental United States beginning with 010 in the upper Northeast. The numbers increase from north to south along the coast and then increase again from south to north with this pattern repeating across the country ending with 997 in Alaska. As is apparent, there was an excellent distribution of treatment directors across the country. Most often, there was a single treatment center in a given ZIP code, but much less frequently two, three, or more were used when deemed necessary based on very large populations or in rural areas where one three-digit ZIP code might cover thousands of square miles. As shown in Figure 2, 45% of the treatment centers were in large urban areas (>250 000), with the remainder in small urban (7.8%), or suburban and rural locations (47.2%).

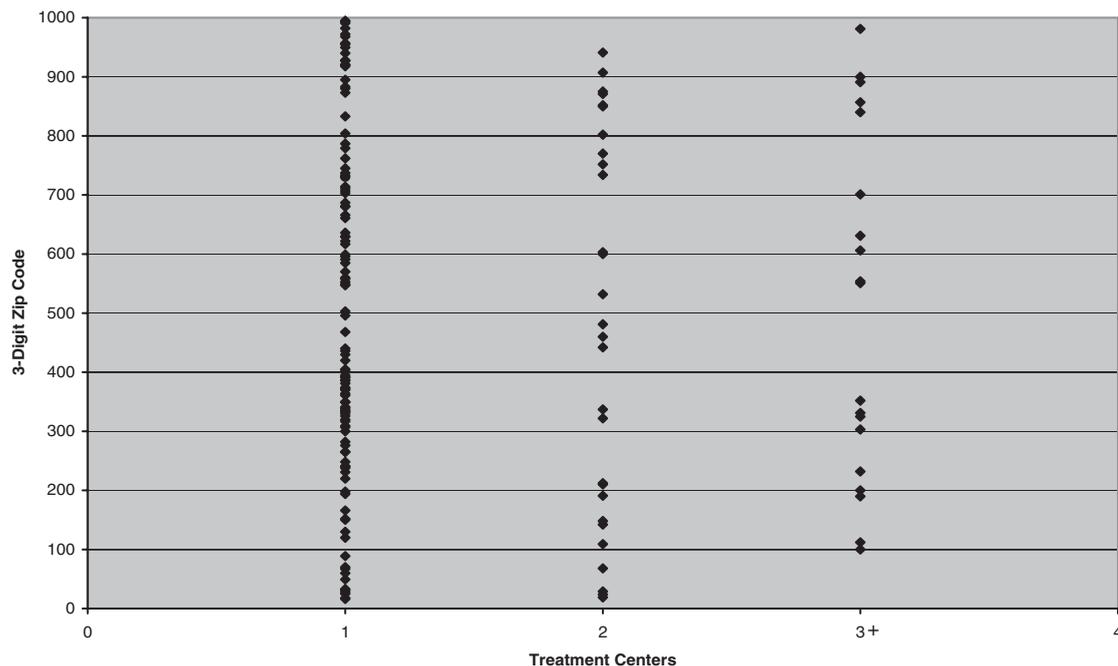**Distribution of Treatment Centers by 3 Digit Zip Code**

Figure 1.   Regional distribution by ZIP code (010-997) for treatment centers participating in this study. The distribution is broken down by 1, 2, or 3+ treatment directors

Patient exposure

In order to correlate cases of abuse with patient exposures we calculated the number of URDDs for each three-digit postal ZIP code in which we had a case of abuse for the eight most commonly used opioid analgesics. Figure 3 shows these data for the period from Quarter 4, 2003 through the end of Quarter 3, 2006. It is obvious that hydrocodone and IR oxycodone products are by far the most prescribed opioid analgesics in our catchment area of 165 ZIP codes. The remainder of the drugs were substantially lower and their rank order was: ER oxycodone > morphine ≅ methadone > fentanyl > hydromorphone > buprenorphine. Although buprenorphine was the least prescribed it should be noted that its use more than doubled from 2005–2006. The introduction of generic ER oxycodone and the fentanyl patch are shown by arrows in Figure 3. There was no measurable change in the rates of prescribing for either of these drugs.

Rates of abuse

Figure 4 shows the rate of abuse, expressed as cases of abuse/1000 patients filling a prescription for an opioid. The abuse of buprenorphine and ER oxycodone were by far the highest, followed closely by hydromorphone and methadone. The rates of abuse of the most widely prescribed opioid analgesics—hydrocodone and IR oxycodone—were extremely low as were all forms of fentanyl. As shown by the arrows in this figure, upon the introduction of generic ER oxycodone and fentanyl there was little change in abuse rates.

Number of abuse cases

Figure 5 shows rates of abuse per 100 000 population for each drug in the ZIP codes we monitored. It is evident that ER oxycodone and hydrocodone products were the most abused drugs of all those studied. The rest of the drugs were much less intensely abused. With the exception of ER oxycodone products, it

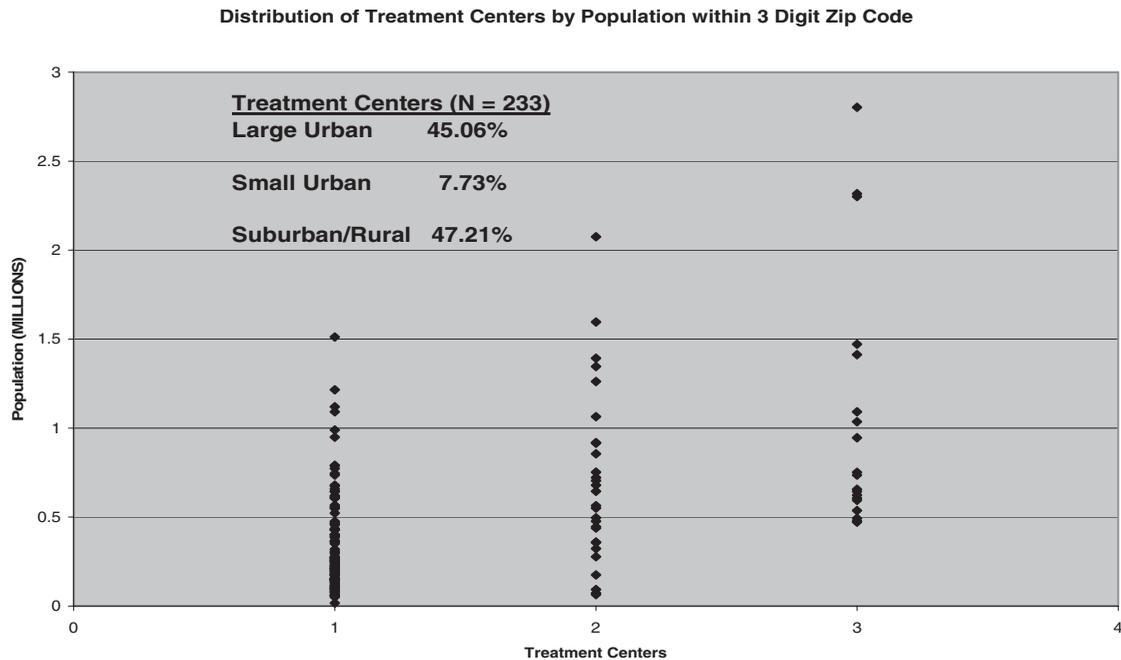**Distribution of Treatment Centers by Population within 3 Digit Zip Code**

Figure 2. Regional distribution of 1, 2, or 3+ treatment directors stratified by the population of the three-digit ZIP codes. Shown as an inset are the percentage of treatment directors in large urban areas (>250 000 population), small urban areas (100 000–250 000 population) and suburban/rural areas (<100 000)

should be noted that the rank ordering of abuse rates within this figure is precisely the opposite of that seen when the data were corrected for degree of exposure. Once again, however, there was no significant effect on abuse rates after the introduction of generic ER oxycodone and the fentanyl patch.

Relationship between exposure and rates of abuse

Figure 6 shows the relationship between the number of abuse cases and URDDs for all of the drugs we studied. The data are the total events—URDDs and abuse cases—for the last four calendar quarters we studied. Two things are obvious from this figure: first, no abuse (0 cases) of opioid analgesics was one of the most prominent responses for at least one quarter of the study for each drug; and, second, high levels of abuse occurred, for the most part, in ZIP codes in which the use was correspondingly high. Table 1 shows the odds ratios of cases being above 5 for a 10-fold increase in the URDDs for each of the eight drugs of interest from the period from 2nd quarter of 2005 to the 1st quarter of 2006. All of the eight odds ratios were significantly greater than 1; they ranged

from 2.3 for hydromorphone to 44.3 for fentanyl. From the data shown in Figure 6 we calculated the rate of abuse which corresponds to the 95th percentile— 1.62 cases/1000 URDDs (1.62%)—such that rates to the left of the line are indices of disproportionately high abuse and were designated as 'signals' of abnormally high abuse relative to exposure.

Location of signals of disproportionately high abuse

Figure 7 shows the number of ZIP codes for each drug which were greater than the 95th percentile for the first Quarter of 2006, and, thus, constitute a signal of disproportionately high abuse. The strongest signals by far occurred for ER oxycodone > buprenorphine ≅ methadone > hydromorphone indicating that the abuse of these drugs relative to therapeutic exposure was disproportionately high in more ZIP codes than the other drug classes. On the other hand, very few signals were found for other drugs, notably the two most commonly used opioid analgesics: IR oxycodone and hydrocodone, indicating their abuse was not disproportionately high
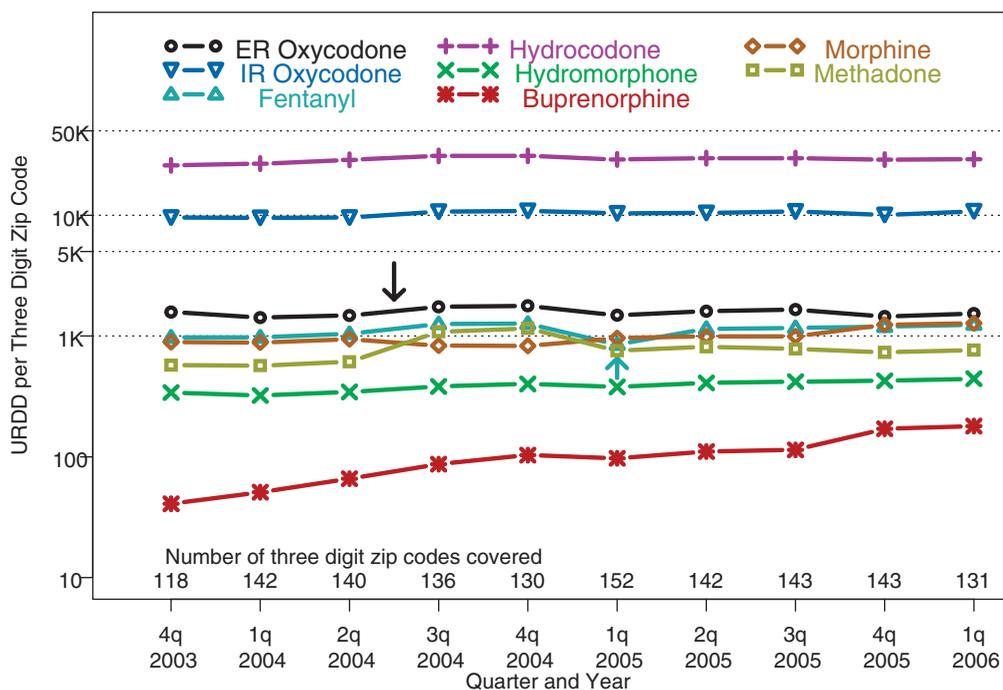
Figure 3.   URDDs in the three-digit ZIP codes for which we had a completed questionnaires, plotted by quarters. The numbers of ZIP codes responding each quarter is found on the *y* axis

relative to exposure. Figure 8 shows a graphical depiction of regions of the country with signals of abuse for one to four of the eight drugs we monitored; Table 2 shows the actual signal sites with the rates of abuse specified. It is apparent that signals of abuse occurred most commonly in small urban and suburban/rural areas, particularly suburban areas of the country's largest cities in the Northeast corridor and the small urban/rural areas of Montana. Relevant to the last point, Table 3 demonstrates that despite a broad representation of treatment centers in all areas of the country, the distribution of the signals of abuse was heavily skewed in the direction of suburban and rural areas.

DISCUSSION

Our data indicate that there is a statistically significant correlation between legitimate, therapeutic exposure to opioid analgesics, and the magnitude of abuse. While this seems logical and intuitive, the relationship has only been inferred previously.[10] What this means, of course, is that in areas in which a drug is used widely for therapeutic purposes there is, unfortunately, a coincident increase in availability to those who use drugs non-therapeutically. It seems reasonable to

assume that a small percentage of every opioid drug prescribed is diverted and used non-therapeutically (e.g., to get high). Thus, when a great deal of drug is prescribed the actual numbers of cases of abuse will rise accordingly. This postulate assumes that the value of a drug for non-therapeutic purposes determines the level of diversion and, as a result, the relative rates of abuse for specific opioid analgesics reflect their abuse liability. It is further assumed that the rate of abuse will remain constant across the country (i.e., abuse rates closely track exposure). If this is true, then if a specific area of the country has disproportionately high levels of abuse, this would suggest that some regionally specific factors make this area unique. The fact that there are, as we have found, signals of high abuse in very discrete loci is not new, since it has been shown for decades that prescription drug abuse (opioids, sedatives, and stimulants) is indigenous to certain areas,[11–14] including the Northeast, and that 'epidemics' of abuse often appear suddenly in as few as three to five cities and then quickly dissipate.

It is noteworthy that the 'signals' of abuse we found in our studies, while present to some extent in larger cities, are for the most part, concentrated in small- to medium-sized urban, suburban, and rural areas. The reasons for this are unclear, but several prominent
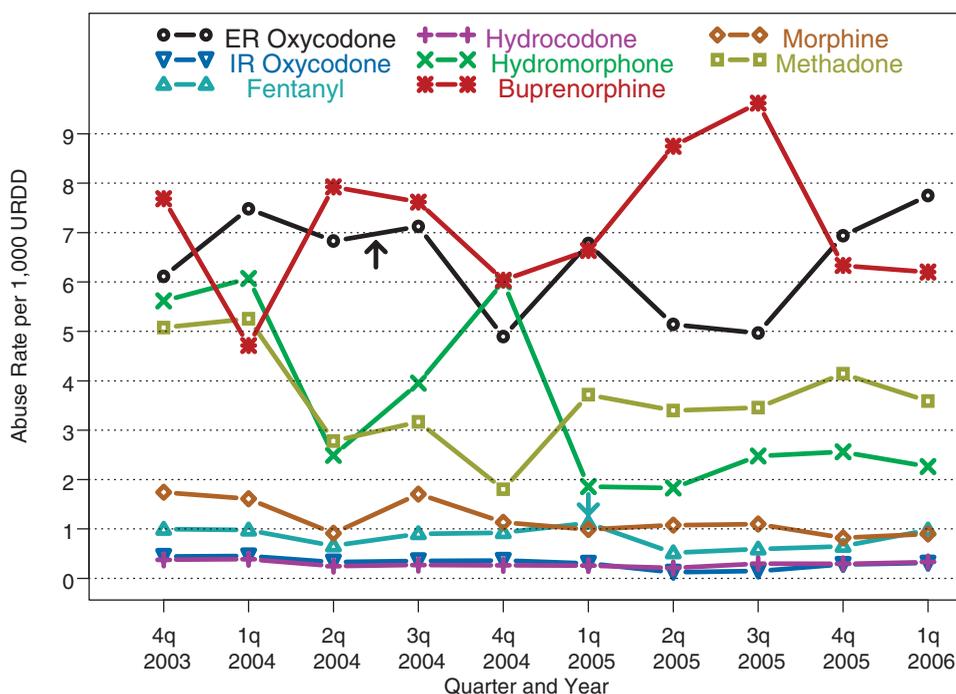
Figure 4.   Rates of abuse, expressed as diagnosed cases of abuse/URDDs for each quarter. The arrows reflect the date of the introduction of generic ER oxycodone and the fentanyl patch

possibilities exist, as suggested in earlier studies[1,2]: first, very cheap heroin is often not readily available in non-urban areas; second, prescription drug abuse has been indigenous for decades in some rural areas[11–14]; third, prescription drugs are often viewed as 'legal', more socially acceptable, and can be obtained relatively easily in much safer locations than heroin; and finally, the cost of prescription drugs at $1–$2/mg may be less of an obstacle to their use in suburban, small urban, and rural areas than it is in the inner cities where financial resources are more limited.

There are other explanations for the regional disparity in signal sites, which may reflect an inherent bias in our studies, and, thus, limit the conclusions. Specifically, other than methadone or other free clinics, drug treatment facilities that require some form of payment may not be readily available in inner cities or may be financially inaccessible for many abusers. However, since nearly half of our treatment centers were located in ZIP codes with very large populations, accessibility seems to be an unlikely factor in the regional disparity we observed. Rather the fact that signal sites were found in non-urban areas could reflect either that: urbanites do not seek

treatment for some reason (e.g., they are recreational users); or the treatment facility was too expensive for the majority of those living in inner cities. While the latter seems most probable, it is not likely to be the sole explanation since we had treatment centers in cities with very large numbers of affluent people (e.g., Manhattan), but there were very low rates of abuse in those areas.

Our observation that therapeutic exposure to a drug leads to corresponding increases in abuse has far-reaching implications vis-à-vis the use of analgesic drugs and the public health. What seems clear is that the public health would not be well served by the simplest conclusion: reducing the therapeutic use of drugs will also reduce abuse. Rather, a risk-benefit ratio needs to be determined for each drug which takes into account the degree of exposure. Most importantly, we believe that this ratio needs to be held constant regardless of exposure. That is, as with all drugs used in medical practice, if a rate of any adverse event of 1 case/1000 URDDs (i.e., 0.1%) is judged to be an acceptable risk-benefit ratio, then this should be true if one thousand or one million patients are legitimately prescribed the drug. This conclusion, of course, is
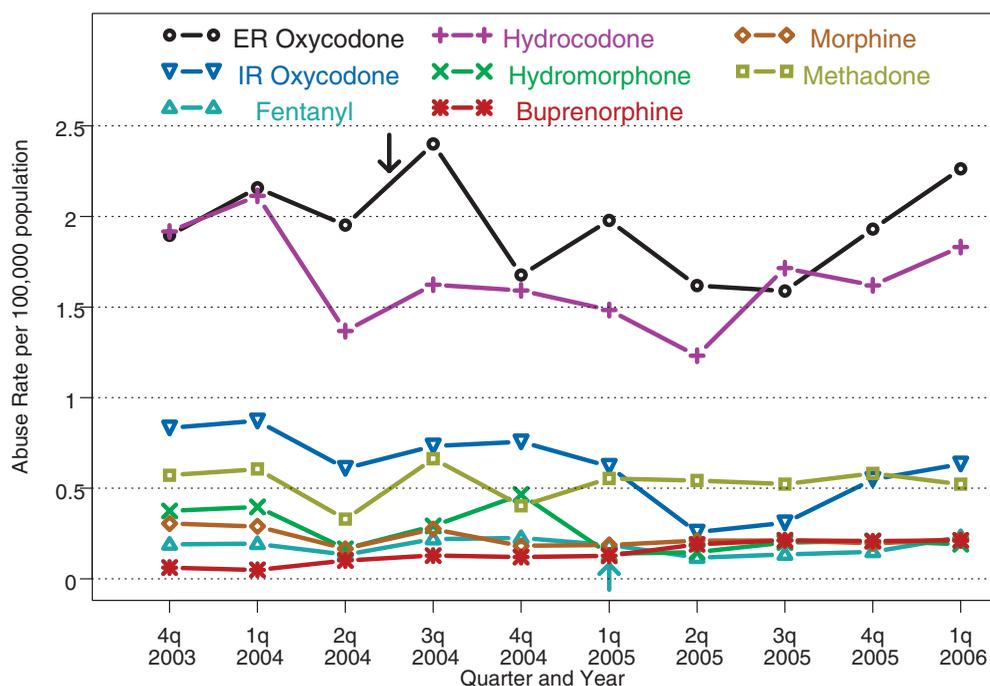
Figure 5.   Rates of abuse, expressed as diagnosed cases of abuse/100 000 population for each quarter. The arrows reflect the date of the introduction of generic ER oxycodone and the fentanyl patch

somewhat dependent on the nature of the adverse event, such as serious cardiovascular problems which might be a life threatening event in a very small group of individuals, but this is a very rare exception to the rule.

The best example of a risk-benefit ratio in which a very large numbers of adverse events occur with very large exposure is that of non-steroidal anti-inflammatory drugs (NSAIDs). In terms of number of adverse events alone, tens of thousands of people experience gastrointestinal bleeds attributable to NSAID's, some of which are fatal (perhaps 15 000 deaths/year) or require hospitalization.[15,16] However, given the fact that these drugs are highly efficacious, they have a favorable risk-benefit ratio and are still widely used in clinical practice. Thus, if drug control policy is based on simply the number of abuse cases and ignores the risk-benefit ratio, this is not only contrary to protecting the public health, but more importantly, places drugs with substance abuse potential in an entirely different category than any other medically used class of drugs.

The rank order of abuse found in this paper shows that ER oxycodone, buprenorphine, hydromorphone, and methadone are the most intensely abused

prescription opioid analgesics, when the data are corrected for degree of exposure and rates are calculated as cases/1000 URDDs.[17,18] Conversely, IR oxycodone and hydrocodone products have very low rates due to their high exposures. On the other hand, if one uses the sheer number of abuse cases expressed as cases/100 000 population, hydrocodone and ER oxycodone are the most heavily abused drugs. The latter observations would very likely conform to what legal authorities and professionals in treatment facilities would conclude are the most abused prescription opioid analgesics in their communities, since on the basis of persons alone, there are certainly very large numbers abusing hydrocodone and oxyco-done products.

The question these quantitative assessments of abuse raise is which rate is the most instructive? It seems apparent to the present authors that a rate of abuse defined as cases/1000 URDDs, is most directly relevant to the all important risk (abuse)-benefit (appropriate analgesia) analysis, which is required in assessments of a drug's safety and efficacy. Never-theless, we acknowledge that it is probably appro-priate, as the FDA (see their Internet web site) has concluded that multiple measures of abuse be used in
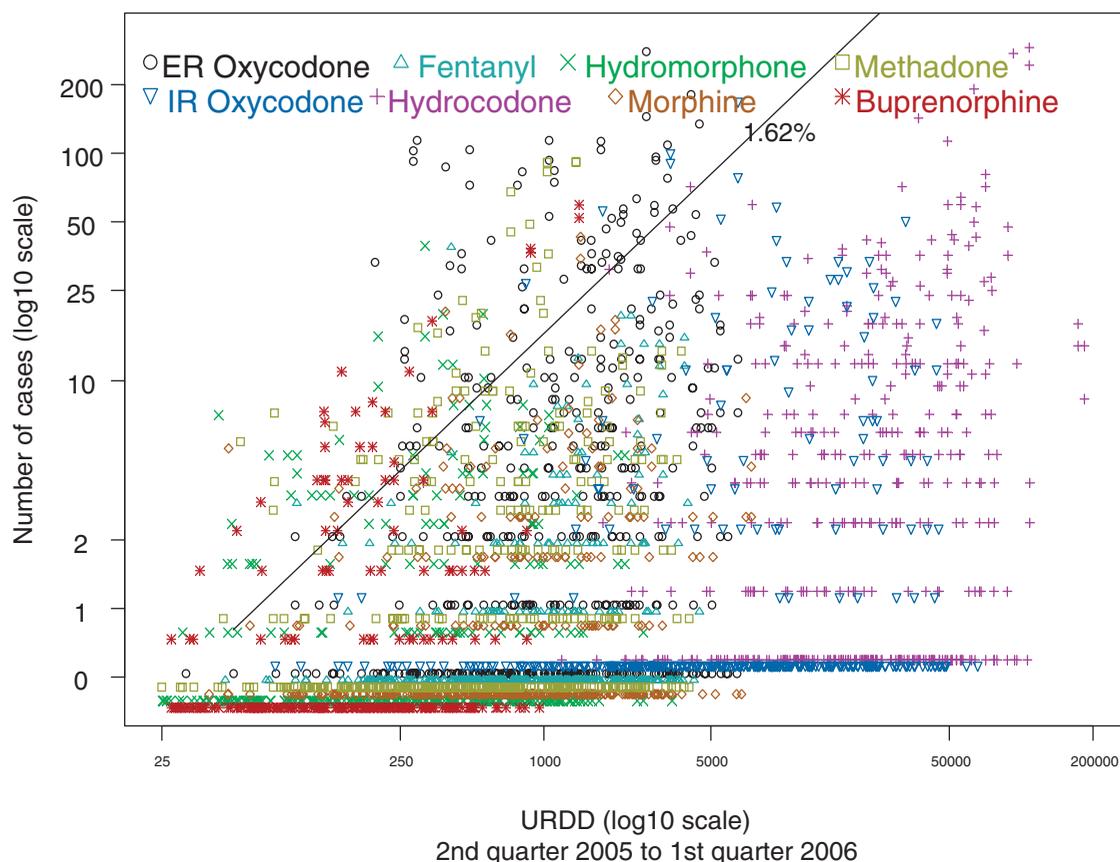
Figure 6. Relationship between number of abuse cases (log10 scale) and URDD (log10 scale) for the 4 quarters between 2nd quarter of 2005 to 1st quarter of 2006. The line represents the 95th percentile rate (1.62 cases of abuse/1000 URDDs) such that any ZIP code to the left of the line was designated as a signal of disproportionately high abuse

evaluating the abuse potential of drugs including the gross number of cases. Thus, we have also presented these data with the realization that the sheer number of abuse cases should not be used exclusively or inappropriately by regulatory agencies in scheduling decisions, which in turn may discourage physician's use of this important class of drugs for pain management.[10] As important, as alluded to above, a risk-benefit ratio cannot be established when only the actual number of abuse cases is considered, since there

Table 1. Results of logistic regression to quantify effect of the magnitude of therapeutic use on the odds of cases of abuse being above five

Drug	N^*	Median URDD	% with cases > 5	OR and 95%CI for 10-fold increase of URDD
ER Oxycodone	558	1116	27.6	4.7 (2.8, 8.0)
IR Oxycodone	559	5836	7.5	2.8 (1.5, 5.4)
Fentanyl	558	939	3.4	44.9 (6.8, 294.6)
Hydrocodone	559	21 967	26.1	4.1 (2.4, 7.0)
Hydromorphine	533	287	5.3	2.3 (1.0, 5.6)
Morphine	558	773	5.0	3.0 (1.1, 7.9)
Methadone	544	518	11.8	3.5 (1.8, 6.7)
Buprenorphine	378	143	5.3	8.5 (2.3, 31.4)

Period: 2nd quarter of 2005 to 1st quarter of 2006.
*# of Zip codes/quarters with URDDs > 25.

Number of Signals with Rate Above the 95th percentile (=1.62)
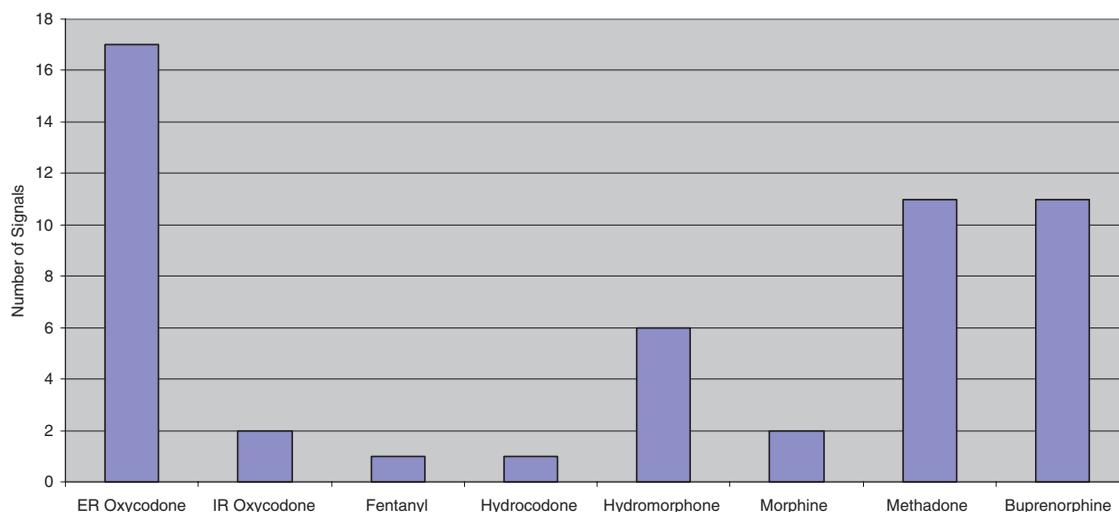**in the 1st Quarter of 2006**

Figure 7.   Number of signals for each drug, defined by a rate of abuse greater than the 95th percentile in the 1st quarter of 2006

is no appropriate denominator relevant to the benefit side of the risk-benefit ratio. As a result, it is unclear how raw or population adjusted numbers alone can be used as the only data relevant to the risk-benefit ratios.

A great deal of previous work on the pharmacoeconomics of drug abuse indicates that as cost decreases, abuse increases and vice versa.[19–22] These data were derived from the use of tobacco, alcohol, and a number of illicit drugs, but the applicability of

these models to prescribed drugs with abuse potential has never been assessed until recently. In a prior report, we documented that the introduction of generic tramadol which was far cheaper than the branded product—Ultram (Ortho-McNeil Pharmaceutical)—had no discernable effect on sales and abuse rates.[2] We cautioned that our results were generated with a drug with very low abuse rates and that street costs may not necessarily be important since the value was quite low
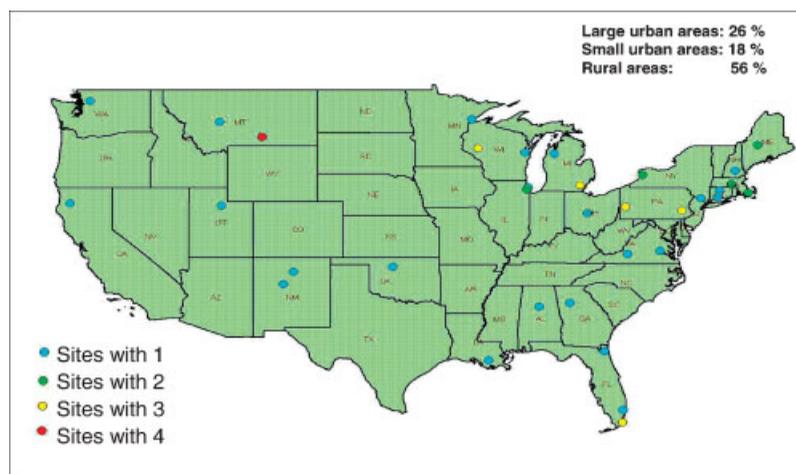

Figure 8.   Location of areas of the country in which 1–4 signals of disproportionately high abuse for any of the 8 opioid analgesics we examined

in any event. Thus, we felt that our results did not conclusively invalidate the intuitive assumption that cheaper generic drugs would lead to more abuse and that this needed to be tested with drugs with very high abuse potential.

Oxycodone and fentanyl, both of which have much higher abuse and diversion levels than tramadol seem to be perfect drugs to assess this hypothesis. We found that the availability of generics at a much reduced price (30% less on average than branded products) had no effect at all on abuse of highly abusable ER oxycodone and fentanyl products. Our data either suggest that the price of a preferred prescription drug entity is irrelevant to abusers of that drug, or that, as suggested in our earlier reports,[2,3] there is a significant 'brand loyalty' among addicts. That is, given the choice, they will pick the familiar branded drug over a less predictable generic which looks very different than the formulation they normally purchase.

Interestingly, we found that the number of people filling prescriptions for ER oxycodone and fentanyl products increased very little with the availability of a cheaper generic, suggesting that drug costs alone do not increase the likelihood that a prescription opioid will be prescribed. However, cost does seem to determine whether a brand name or generic is used, which is often dictated by medical insurance companies.[3] This conclusion and our supporting data seem to be at variance with the existing literature[23–39] that suggests that the price of prescription drugs greatly impacts patient access to these drugs. We have no explanation for why our data seem to suggest that this may be untrue for opioid analgesics, but this clearly needs to be examined in more depth.

The very high rates of buprenorphine and metha-done abuse, the only drugs approved for use in the treatment of opioid addiction, found in our studies is a matter of great concern, particularly with the large number of physicians who are now using buprenor-phine in office-based treatment of opioid addiction. These prescribers should be mindful of its potential to be diverted and misused, particularly since the population for whom buprenorphine and methadone are intended consists of polysubstance abusers with extensive histories of opioid abuse. As a result, diversion of some of legitimately prescribed medi-cations should not be unexpected, but should be recognized as a real possibility. Nonetheless, these rates are very high and abuse needs to be monitored carefully over the next 12–18 months.

A limitation in our approach is that we may have found abuse because we had a treatment center in a specific location. This is undoubtedly true to some extent, but in terms of our most important conclusion, we compared abuse and therapeutic exposure across a spectrum of large and small ZIP codes which are representative of all ZIP codes across the country. Thus, given that we surveyed almost 20% of the nation's ZIP codes, it is difficult to see how the relative rates of abuse we found and the relationship between abuse and therapeutic exposure would deviate significantly in the total national population from results obtained in our sample.

An additional concern is that our selected treatment centers only participated when they had a case of abuse to report, which would thus overstate the numbers and incidence of rate of abuse, i.e., treatment centers only responded 'yes' when they had a case of abuse and failed to report no cases of abuse for a specific drug class. While we cannot eliminate this as a factor in our results completely, it should be noted that the most common response from treatment centers was no cases of abuse in their quarterly reports (Figure 6), for at least some opioids in one or more quarters. This suggests that a bias toward over-reporting may not exist, but that the centers are consistently providing information on abuse cases of all eight opioid analgesics individually.

In conclusion, our results demonstrate that there is an excellent correlation between therapeutic exposure to opioid analgesics and their abuse. This is certainly not a unique property of opioid analgesics since all drugs have adverse events which increase in number as more patients are prescribed the medication. Thus, proper medical practice dictates that before a drug is used a risk-benefit ratio should be constructed which balances the efficacy of the drug against its adverse events. The most meaningful index of the safety of the drug and the tolerability of adverse events is: number of adverse events/1000 people using the drug therapeutically. Obviously, the lower the rate the safer the drug but, most importantly, this ratio places the incidence of adverse events in perspective by correcting for exposure. We argue that the same risk-benefit analysis should be applied to opioid analgesics, but unfortunately all too often regulatory agencies, such as the FDA and DEA, focus solely on the numbers of cases of abuse, non-corrected for exposure, in the control of these medications. This treats opioid analgesics differently than all other drugs and seems not only scientifically and clinically indefensible, but contributes to the undertreatment of pain in this country by overstating the incidence of abuse which in turn nurtures 'opioidphobia' among physicians. We believe the rate of abuse described in this paper—cases of abuse per thousand patients using

Table 2. Three-digit Zip codes with rates above the 95th percentile (=1.62 cases/1000 URDDS) in the 1st quarter of 2006

Location	3-digit Zip code	ER Oxycodone	IR Oxycodone	Fentanyl	Hydrocodone	Hydromorphone	Morphine	Methadone	Buprenorphine
Worcester, MA	016	31.4	2.4						
Buzzards Bay, MA	025	20.5							
Concord, NH	033	3.3							
Waterville, ME	049	6.6							2.3
Manchester, CT	060							1.8	
New Haven, CT	065					2.2			
Middletown, NY	109							1.8	
Buffalo, NY	142	2.8							
Warrendale, PA	150	1.9						1.8	2.6
Adamstown, PA	195	6.4				3.3		11.2	
Richmond, VA	232								3.0
Roanoke, VA	240								2.2
Atlanta, GA	303								2.7
Jacksonville, FL	322	2.9							
Pompano Beach, FL	330	3.2						6.9	2.9
Fort Lauderdale, FL	333								2.1
Birmingham, AL	352					9.9			
Newark, OH	430								3.1
Ann Arbor, MI	481	5.2						7.4	5.8
Traverse City, MI	496	2.4							
Eau Claire, WI	547	37.4	2.8				2.4		3.0
Duluth, MN	558							4.1	
Billings, MT	591	9.9		9.8		15.8		2.5	
Helena, MT	596					3.3			
Evanston, IL	602							2.2	
Oak Park, IL	603	2.2				2.1			
Houma, LA	703	4.6							
Enid, OK	737						2.3		
Sandy, UT	840	4.2							
Albuquerque, NM	871							4.0	
Santa Fe, NM	875							3.6	
Eureka, CA	955								
Everett, WA	982	2.0							3.7

Table 3. Signal sites and treatment center distribution

	Treatment directors (%)	Signal sites (%)
Large urban	45.06	26
Small urban	7.73	18
Suburban/rural	47.21	56

the drug—best describes the risk-benefit ratio of this vitally important class of drugs and should be used as the basis for evidence-based medical use of these drugs.

KEY POINTS

- Risk-benefit analyses are required for all drugs, including opioid analgesics, which need to be evaluated in the regulation and therapeutic use of this important class of drugs.
- There is an excellent correlation between therapeutic exposure to opioid analgesics and their subsequent abuse.
- Abuse of buprenorphine, oxycodone, hydro-morphone, and methadone are disproportionately high relative to other opioid analgesics.
- Risk-management programs that meet FDA expectations can be effectively implemented.
- Prescription drug abuse is common across the United States, but is most prevalent in rural areas and small urban regions.

REFERENCES

1. Cicero TJ, Adams EH, Geller A, et al. A post-marketing surveillance program to monitor Ultram (tramadol hydrochloride) abuse in the United States. Drug Alcohol Depend 1999; 57: 7–22.
2. Cicero TJ, Inciardi JA, Adams EH, et al. Rates of abuse of tramadol remain unchanged with the introduction of new branded and generic products: results of an abuse monitoring system—1994–2004. Pharmacoepidemiol Drug Saf 2005; 14: 851–859, Published online 5-12-05 in Wiley Interscience, www.interscience.wiley.com . DOI: 10.1002/pds.1113
3. Cicero TJ, Inciardi JA, Munoz A. Trends in abuse of OxyContin and other opioid analgesics in the United States: 2002–2004. J Pain 2005; 6: 662–672.
4. Government Accounting Office (GAO) Report to Congressional Requesters. Prescription Drugs: OxyContin abuse and diversion and efforts to address the problem. December 2003; GAO-04-0110.
5. Substance Abuse and Mental Health Services Administration. Results from the 2002 National Survey on Drug Use and Health: National Findings. Office of Applied Studies, NHSDA Series: H22, DHSS Publication No. SMA 03-3836, 2003; Rockville, MD.
6. Substance Abuse and Mental Health Services Administration. Emergency Department Trends from the Drug Abuse Warning Network, Final Estimates 1995–2002. Office of Applied Studies. 2003; NHSDA Series: D-24, DHSS Publication No. SMA 03-3780, Rockville, MD.
7. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. N Engl J Med 1999; 340: 1888–1899.
8. Thomson Health Care, Inc. The PDR Pocket Guide to Prescription Drugs (5th edn), The Pdr; Paperback. Medical Economics Company, Inc., Pocket Books: New York, 2002.
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (4th edn), American Psychiatric Association: Washington, DC, 1994.
10. Sapienza FL. Abuse deterrent formulations and the Controlled Substances Act (CSA). Drug Alcohol Depend 2006; 83 (Suppl 1): S23–30.
11. Inciardi JA, Goode JL. OxyContin and prescription drug diversion. Consumer Res 2003; 22–25.
12. Joranson DE, Ryan KM, Gilson AM, et al. Trends in medical use and abuse of opioid analgesics. JAMA 2000; 283: 1710–1714.
13. US Dept. of Justice Drug Enforcement Administration Diversion Control Program. August 11, 2004. Prescription Pain Medication: Frequently Asked Questions and Answers for Health Care Professionals and Law Enforcement Personnel. http://www.deadiversion.usdoj.gov/new.htm
14. Zacny J, Bigelow G, Compton P, et al. College on problems of drug dependence taskforce on prescription opioid non-medical use and abuse: position statement. Drug Alcohol Depend 2003; 69: 215–232.
15. Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. J Rheumatol 1999; 56: 18–24.
16. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. N Engl J Med 1999; 340: 1888–1899.
17. Cicero TJ, Inciardi JA. Diversion and abuse of methadone prescribed for pain management. JAMA 2005; 293: 297–298.
18. Cicero TJ, Inciardi JA. Abuse potential of Buprenorphine in office-based treatment of opioid dependence. N Engl J Med 2005; 353: 1863–1865.
19. Caulkins JP. Drug prices and emergency department mentions for cocaine and heroin. Am J Public Health 2001; 91: 1446–1448.
20. Hyatt RR, Jr., Rhodes W. The price and purity of cocaine: the relationship to emergency room visits and death, and to drug use among arrestees. Stat Med 1995; 14: 655–668.
21. Petry NM. A behavioral economic analysis of polydrug abuse in alcoholics: asymmetrical substitution of alcohol and cocaine. Drug Alcohol Depend 2001; 62: 31–39.
22. Sloan FA, Reilly BA, Schenzler C. Effects of prices, civil and criminal sanctions, and law enforcement on alcohol-related mortality. J Stud Alcohol 1994; 4: 454–465.
23. Brian EW, Gibbens SF. California's Medi-Cal co-payment experiment. Med Care 1974; 12: 1–56.
24. Campo K, De Satebel O, Gijsbrechts E, et al. Physicians' decision process for drug prescription and the impact of pharmaceutical marketing mix instruments. Health Mark Q 2005; 22: 73–107.
25. DeWitt EM, Glick HA, Albert DA, et al. Medicare coverage of tumor necrosis factor α inhibitors as an influence on physicians' prescribing behavior. Arch Intern Med 2006; 166: 57–63.
26. Federman AD, Adams AS, Ross-Degnan D, et al. Supplemental insurance and use of effective cardiovascular drugs

among elderly medicare beneficiaries with coronary heart disease. *JAMA* 2001; **286**: 1732–1739.

27. Goldman DP, Joyce GF, Escarce JJ, *et al*. Pharmacy benefits and the use of drugs by the chronically ill. *JAMA* 2004; **291**: 2344–2350.

28. Harris BL, Stergachis A, Ried LD. The effect of drug co-payments on utilization and cost of pharmaceuticals in a health maintenance organization. *Med Care* 1990; **28**: 907–917.

29. Nelson AA, Reeder CE, Dickson WM. The effect of a Medicaid drug copayment program on the utilization and costs of prescription services. *Med Care* 1984; **22**: 724–736.

30. Piette JD, Heisler M, Wagner TH. Cost-related medication under-use among chronically ill adults: the treatments people forego, how often, and who is at risk. *Am J Public Health* 2004; **94**: 1782–1787.

31. Piette JD, Heisler M, Horne R, *et al*. A conceptually based approach to understanding chronically ill patients' responses to medication cost pressures. *Soc Sci Med* 2006; **62**: 846–857.

32. Reeder CE, Nelson AA. The differential impact of copayment on drug use in a Medicaid population. *Inquiry* 1985; **22**: 396–403.

33. Safran DG, Neuman P, Schoen C. Prescription drug coverage and seniors: how well are states closing the gap? *Health Aff (Millwood)* 2002; W253–W268.

34. Sagall RJ. Can your patients afford the medications you prescribe? *Fam Pract Manag* 2006; **13**(4): 67–69.

35. Steinman MA, Sands LP, Covinsky KE. Self-restriction of medications due to cost in seniors without prescription coverage. *J Gen Intern Med* 2001; **16**: 793–799.

36. Stuart B, Grana J. Ability to pay and the decision to medicate. *Med Care* 1998; **36**: 202–211.

37. Soumerai SB, Avorn J, Ross-Degnan D, *et al*. Payment restrictions for prescription drugs under Medicaid: effects on therapy, cost, and equity. *N Engl J Med* 1987; **317**: 550–556.

38. Tamblyn R, Laprise R, Hanley JA, *et al*. Adverse events associated with prescription drug cost-sharing among poor and elderly persons. *JAMA* 2001; **285**: 421–429.

39. Tseng W, Brook RH, Keeler E, *et al*. Cost-lowering strategies used by Medicare beneficiaries who exceed drug benefit caps and have a gap in drug coverage. *JAMA* 2004; **292**: 952–960.