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

Theodore J. Cicero PhD1*, Hilary Surratt PhD2, James A. Inciardi PhD2 and Alvaro Munoz PhD3

1Washington University School of Medicine, MO, USA
2University of Delaware, Coral Gables, FL, USA
3Johns 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 literature7 that to our knowledge has never been addressed with any scientific data: that the abuse of opioid analgesics...
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, \( \text{rate} \), 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, 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 (\( \pm 10\% \)) 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
and drugs with disproportionately high rates, divided by URDDs. To identify three-digit ZIP codes
(i.e., informant reported number of abuse cases
for each drug in each quarter), we 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
great 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%).
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
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.
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. 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, 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
possibilities exist, as suggested in earlier studies\textsuperscript{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\textsuperscript{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
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. 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. 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 oxycodone 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. Nevertheless, we acknowledge that it is probably appropriate, as the FDA (see their Internet web site) has concluded that multiple measures of abuse be used in

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.\(^\text{10}\) 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 is no way to determine the relative risk of abuse for any given drug or class of drugs.

### 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.

### 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>N(^\text{a})</th>
<th>Median URDD</th>
<th>% with cases &gt; 5</th>
<th>OR and 95%CI for 10-fold increase of URDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER Oxycodone</td>
<td>558</td>
<td>1116</td>
<td>27.6</td>
<td>4.7 (2.8, 8.0)</td>
</tr>
<tr>
<td>IR Oxycodone</td>
<td>559</td>
<td>5836</td>
<td>7.5</td>
<td>2.8 (1.5, 5.4)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>558</td>
<td>939</td>
<td>3.4</td>
<td>44.9 (6.8, 294.6)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>559</td>
<td>21 967</td>
<td>26.1</td>
<td>4.1 (2.4, 7.0)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>533</td>
<td>287</td>
<td>5.3</td>
<td>2.3 (1.0, 5.6)</td>
</tr>
<tr>
<td>Morphine</td>
<td>558</td>
<td>773</td>
<td>5.0</td>
<td>3.0 (1.1, 7.9)</td>
</tr>
<tr>
<td>Methadone</td>
<td>544</td>
<td>518</td>
<td>11.8</td>
<td>3.5 (1.8, 6.7)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>378</td>
<td>143</td>
<td>5.3</td>
<td>8.5 (2.3, 31.4)</td>
</tr>
</tbody>
</table>

\(^\text{a}\)\# of Zip codes/quarters with URDDs > 25.
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. 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. 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.
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, 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. This conclusion and our supporting data seem to be at variance with the existing literature 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 analogics, but this clearly needs to be examined in more depth.

The very high rates of buprenorphine and methadone 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 buprenorphine 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 medications 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 analogics individually.

In conclusion, our results demonstrate that there is an excellent correlation between therapeutic exposure to opioid analogics and their abuse. This is certainly not a unique property of opioid analogics 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 analogics, 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 analogics 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—a 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

<table>
<thead>
<tr>
<th>Location</th>
<th>3-digit Zip code</th>
<th>ER Oxycodone</th>
<th>IR Oxycodone</th>
<th>Fentanyl</th>
<th>Hydrocodone</th>
<th>Hydromorphone</th>
<th>Morphine</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worcester, MA</td>
<td>016</td>
<td>31.4</td>
<td>2.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Buzzards Bay, MA</td>
<td>025</td>
<td>20.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concord, NH</td>
<td>033</td>
<td>3.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waterville, ME</td>
<td>049</td>
<td>6.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manchester, CT</td>
<td>060</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.3</td>
</tr>
<tr>
<td>New Haven, CT</td>
<td>065</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.2</td>
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<tr>
<td>Middletown, NY</td>
<td>109</td>
<td></td>
<td></td>
<td>2.2</td>
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<td></td>
<td></td>
<td></td>
<td>1.8</td>
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<tr>
<td>Buffalo, NY</td>
<td>142</td>
<td>2.8</td>
<td></td>
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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, hydromorphone, 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**


