*Original Article*

# A Comparison of the Abuse Liability of Tramadol, NSAIDs, and Hydrocodone in Patients with Chronic Pain

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## Abstract
*Concern about abuse/dependence in chronic pain patients taking opioid analgesics may lead
to undertreatment of pain, yet little is known about the prevalence of abuse/dependence in
these patients and how it differs among analgesic agents. The objective of this study was to
assess the prevalence of tramadol abuse compared to nonsteroidal anti-inflammatory drugs
(NSAIDs) and hydrocodone-containing analgesics in patients with chronic noncancer pain
(CNP). The study had three arms. The first arm consisted of subjects prescribed tramadol
alone; the second of subjects randomized to either NSAIDs or tramadol; and the third of
subjects randomized to hydrocodone or tramadol. Each investigator received two boxes of
prescriptions randomized so that one in every four prescriptions was for tramadol. Upon
deciding on the therapeutically appropriate arm, the physician selected the appropriate box,
opened the next envelope and completed the enclosed prescription. After the initial
randomization, physicians could prescribe whatever medication was therapeutically
appropriate. A total of 11,352 subjects were enrolled. Up to nine interviews using
a structured questionnaire were conducted over a 12-month period. An algorithm called the
"Abuse Index" was developed to identify subjects who were abusing the drug. The primary
components of the index were increasing dose without physician approval, use for purposes
other than intended, inability to stop its use, and withdrawal. The percent of subjects who
scored positive for abuse at least once during the 12-month follow-up were 2.5% for NSAIDs,
2.7% for tramadol, and 4.9% for hydrocodone. When more than one hit on the algorithm
was used as a measure of persistence, abuse rates were 0.5% for NSAIDs, 0.7% for*

*tramadol, and 1.2% for hydrocodone. Thus, the results of this study suggest that the prevalence of abuse/dependence over a 12-month period in a CNP population that was primarily female was equivalent for tramadol and NSAIDs, with both significantly less than the rate for hydrocodone.*   J Pain Symptom Manage 2006;31:465–476. © 2006 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

### Key Words

*Tramadol, hydrocodone, nonsteroidal anti-inflammatory drugs, prevalence of abuse, pain, independent steering committee, analgesics, questionnaire*

## Introduction

Tramadol is a centrally-acting analgesic with weak μ-opioid agonist properties and weak inhibition of norepinephrine and serotonin reuptake. It has been marketed in Germany without controls by Grünenthal since 1977, where it has been one of the most widely prescribed analgesics. Preclinical,[1–4] clinical,[5–7] and epidemiologic[8] studies prior to 1994 suggested that tramadol had a low abuse liability, which led the Drug Abuse Advisory Committee (DAAC) to recommend to the U.S. Food and Drug Administration (FDA) that tramadol be approved as a nonscheduled analgesic.[9] This decision was based not only on the anticipated low abuse but the recognition that pain is often undertreated and that physicians are less likely to prescribe scheduled analgesics,[10–13] especially for chronic pain. The decision of the DAAC was, however, contingent on establishing an Independent Steering Committee (ISC) and a proactive postmarketing surveillance program as a protective measure to detect unexpectedly high abuse.

The proactive program that was developed consisted of two Phase IV studies and a proactive surveillance program designed to rapidly assess any unexpected levels of tramadol abuse.[14] One Phase IV study consisted of a study of abuse among impaired health professionals,[15] whereas the second study, which is the subject of this report, examined abuse in patients with chronic noncancer pain (CNP).

Although a number of studies suggested that the risk of abuse or dependence in pain patients taking opioid analgesics is rare,[16,17] few data are available on the prevalence of abuse among patients taking opioid analgesics over extended periods of time for chronic pain. To our knowledge, the study described in this paper, which used more than 11,000 patients, represents the largest effort to systematically estimate the prevalence of opioid analgesic abuse in patients with CNP.

Estimates of the prevalence of opioid abuse/dependence in the studies that have been conducted in CNP patients vary widely and range from 0% to more than 30%.[18–20] One reason for these inconsistent results may be that a variety of measures were used, some of which may have been inappropriate for diagnosing abuse in chronic pain patients. For example, Fishbain et al. noted that of the 24 studies they reviewed, only seven used acceptable diagnostic criteria and definitions for substance-use disorders.[20] Of these, only three attempted to address the concepts of psychological dependence and compulsive use that are the defining features of dependence ("addiction"), and they ranged from 3% to 16%.

Current instruments such as the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV®) Axis 1 Disorders and the Composite International Diagnostic Interview are based upon DSM-IV-Text Revision (TR)® criteria and are used to determine the prevalence of abuse and dependence in epidemiologic and treatment outcome studies, and in clinical practice.[21–23] However, it has been suggested that the application of DSM-IIIR® and/or DSM-IV-TR® criteria in patients with chronic pain could result in a large number of false positives.[23–26] Thus, a consensus document entitled "Definitions Related to the Use of Opioids for the Treatment of Pain" reintroduced the term "addiction," which is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.[27] Behaviors suggestive of addiction

include inability to take medications according to an agreed upon schedule, taking multiple doses together, isolation from family and friends, use of analgesic medications for other than analgesic effects such as sedation, anxiety, or intoxication.[27] The questionnaire used in this study included several of these indices.

A problem encountered in the design of this study was that there were no standardized scales or norms against which to compare tramadol abuse, if it occurred, with abuse of other substances with higher and lower abuse potential. As a result, a decision was made to compare the abuse/dependence associated with tramadol to a negative comparator, nonsteroidal anti-inflammatory drugs (NSAIDs), and to a positive comparator, hydrocodone-containing analgesics. The NSAID analgesics were chosen because they were considered to have almost no abuse liability while the positive comparator, hydrocodone-containing analgesics, were widely recognized as being abused albeit not primarily among chronic pain patients.[28,29]

The hypothesis underlying this study was that abuse/dependence associated with tramadol would not be higher than the negative control (NSAIDs) and would be lower than the positive control (hydrocodone-containing analgesics).

## Methods

### Design of Prospective Study

The initial study design required recruiting 12,000 subjects: 4000 subjects assigned to each of the comparator drugs (4000 taking tramadol, 4000 taking NSAIDs, and 4000 taking hydrocodone-containing analgesics). Because interviews with physicians indicated that they were unwilling to prescribe NSAIDs or hydrocodone-containing analgesics in the same arm, the study had three arms (Fig. 1). The first arm consisted of subjects prescribed tramadol alone; the second of subjects randomized to either NSAIDs or tramadol; and the third, subjects randomized to hydrocodone-containing analgesics or tramadol. The tramadol alone arm was proposed because there were conditions in which NSAIDs were contraindicated (e.g., gastrointestinal bleeding) and since this would be a target population, we did not want them excluded from the study. Physicians could enter up to six of these

subjects in the study. An attrition rate of 25% was anticipated, resulting in a projected final sample of 9000 subjects or 3000 in each arm. The final distribution after randomization is seen in Fig. 1.

The selection of the appropriate arm was based on medical history and the presenting pain complaint. Each investigator received two boxes of envelopes, one containing tramadol and NSAID prescription blanks and the other containing hydrocodone and tramadol prescription blanks. The prescriptions were randomized so that one in every four prescriptions was for tramadol. Upon deciding which arm comprised the best clinical fit for the subject, the physician simply picked the appropriate box, opened the next envelope and completed the prescription that was enclosed. If the physician chose not to randomize a patient to the study but to enter the subject into the tramadol only arm, the physicians' own prescription blank was used rather than one from the randomized sets. This maintained the one in four ratios for the randomized arms.

Randomization occurred at the initiation of the study. Once the subject was enrolled, it became a natural history study, in that physicians could prescribe whatever medication was therapeutically appropriate based on response to the initial medication; thus, some subjects may have been taking NSAIDs, hydrocodone, or tramadol at different times during the study. All data were collected and analyzed by the drug the subject was taking at the time of the interview not the drug to which they were randomized. All subjects were tracked for 12 months (9 interviews—at baseline, 2 weeks, 1 month, 2 months, 3 months, 4 months, 6 months, 9 months, and 12 months) unless it no longer became possible to establish contact, e.g., moving without notification or requests to drop out of the study.

### Patient Eligibility

Subjects must have had chronic (≥4 months) nonmalignant pain (excluding headaches) as the primary complaint and be 18–74 years of age. They must also have been initiating a new therapy that included a prescription for one of the reference medications. All subjects signed an informed consent and were paid either $5 or $10 per completed interview based on its length.
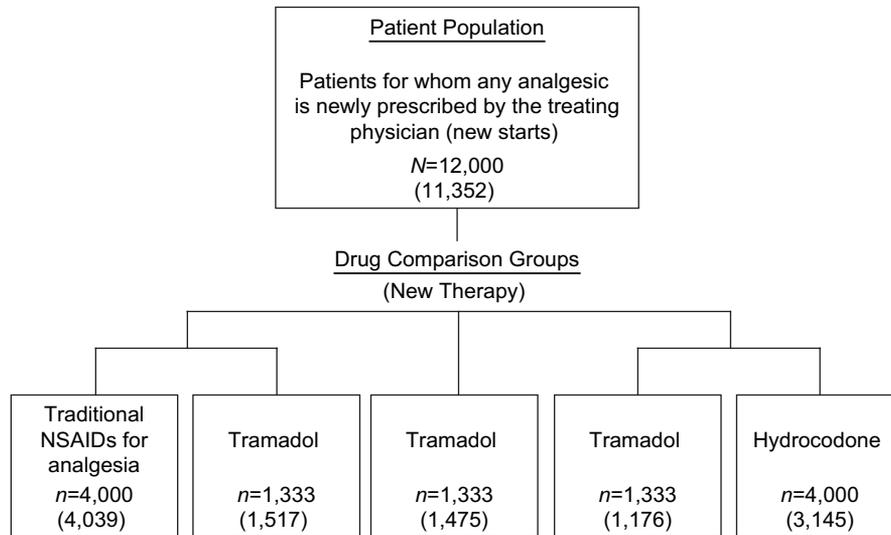
Fig. 1. Subject population, drug comparison groups. Numbers in parentheses are the actual numbers achieved vs. the target numbers.

Subjects were excluded if they had a hearing or speech impediment, a serious mental disturbance (e.g., psychotic or suicidal), or a current substance abuse problem. Physicians used their own judgment in determining if a potential subject had a current substance abuse problem. Subjects were also excluded if they were taking any contraindicated medications (e.g., other opioids) or had a condition that would preclude use of any of the study medications.

### Computer-Assisted Telephone Interviewing

Harris Interactive, a national research company, completed interviews via a computer-assisted telephone interview and interviewers were trained in the international ISO 9002 quality standards (www.iso.ch/iso/en/ISOOnline). All interviewers completed 3 days of training in use of the computer system, transcribing verbatim comments, phrases, callbacks, and mock interviews. Interviewers were also trained to probe on certain responses to clarify responses that might otherwise appear to suggest abuse. For example, if a subject responded that it "was hard to stop taking their medication," they were asked to further explain their answer. If the subjects' response indicated therapeutic intent, such as their pain would come back, that response was not counted in the algorithm. If, on the other hand, their response was not related to therapeutic intent, such as they felt that they were

becoming addicted, it was counted. Interviewers were monitored on a regular basis to ensure that the protocol was being followed and to identify any training issues.

Two variations of the questionnaire were used. The full questionnaire (long form) included assessments of medication use, physical function, emotional function, and pain intensity. A shorter version (short form) did not include evaluations of physical and emotional functions. The long questionnaire was administered at baseline, 2, 6, and 12 months. The short version was administered at 2 weeks, 1, 3, 4, and 9 months.

### Questionnaire

A questionnaire designed specifically for chronic pain patient populations was developed, based on the available literature and expert consultation including input from the ISC. It was based on a conceptual model that identified the following four distinguishable but overlapping features of chronic pain: medication usage (including abuse and dependence), physical functioning, emotional functioning, and pain intensity.[30–32]

The questionnaire was pretested among three overlapping replicates of 10 patients in an iterative manner to ensure that it would be understandable to subjects and to eliminate redundancy. The resulting questionnaire was administered to a pilot sample of 194 chronic

pain patients taking either NSAIDs or opioids. The results were analyzed to determine the reliability and validity of various components prior to implementation.

Among the medication usage questions were "Increasing the dose of medication without physician approval, problems trying to stop or cut down, use for purposes other than intended (i.e. anxiety or when feeling depressed)." Separate questions were asked about feeling intoxicated or being in a good mood.[27,33,34] Because of the relationship between smoking, drinking, and drug use, questions on these behaviors were included in the questionnaire to further define the characteristics of the population.[35–39]

### Withdrawal Score

A 24-item set of questions used at the NIDA Addiction Research Center, Study 219 (ARC 219) was used. There was no absolute value that indicated clinically significant withdrawal; rather, the scores were compared to each other. Since physical dependence is expected in long-term treatment with opioids, withdrawal without evidence of inappropriate use and loss of control was not considered problematic. Withdrawal was included because it is one of the signs of dependence and also because the FDA and U.S. Drug Enforcement Administration still consider withdrawal an indicator in scheduling decisions.[40,41] Withdrawal is considered because Factor 7 of the eight factor analysis under the Controlled Substance Act is "its psychic or physiological dependence liability," and withdrawal is the measure of physiological dependence.[40]

### Pain Intensity

Pain intensity was measured with a 0–10 numeric rating, an accepted valid measurement of pain intensity.[42] Subjects rated both their current level of pain and average level of pain over the past week from 0 (no pain) to 10 (worst pain). Pain scores were collected at each interview. Bodily pain scores are one of the subscales of the SF-36, which were collected four times during the study.[43–45]

### Algorithm

For the purposes of the study, the ISC developed an "Abuse Index," which was conceptually based on existing classification systems for abuse and dependence (i.e., DSM-IV-TR®), as well as potential measures of abuse and dependence suggested by other studies.[23,27,33,34] A "case" identified using the Abuse Index was also referred to as a "hit."

Four dimensions were identified:

- Inappropriate use (increasing dose without physician approval)
- Use for purposes other than intended (anxiety and depression plus good mood and feeling intoxicated)
- Inability to stop use (loss of control)
- Evidence of opioid withdrawal (Withdrawal Score)

One point was given for a positive score on each dimension. The Withdrawal Score was only obtained if the subject had discontinued his or her medication, which was operationalized as not having taken his or her medication in the last 48 hours. A case of presumptive abuse or dependence was based upon 2 out of 3 points if the Withdrawal Score was not obtained or 3 out of 4 points if it was obtained.

Physical dependence is an expected outcome of prolonged opioid therapy, but addiction is not. Addiction is characterized by loss of control or compulsive drug use.[27] The first three measures in the abuse algorithm are consistent with measures of loss of control subsequently published in a consensus document referred to previously.[27]

Since a prospective study such as this had not been done before in a large patient population, we did not attempt to create the survey instrument as an absolute diagnostic tool. Rather the Abuse Index was designed as a relative scale and was used to provide comparative results with the other medications. The purpose was to estimate whether the scores on the Abuse Index were the same, less than, or greater than the score of comparative medications on the same scale. The algorithm in Table 1 was used to identify cases.

When a subject responded to the interviewer in a way that might suggest that he or she could be included as a case based on the algorithm, further probes were initiated, as previously described, to ascertain whether the subject should be included as a potential case or not.

*Table 1*
**Abuse Index Algorithm**

| Score | |
|---|---|
| 1 | Inappropriate use |
| | If the subject met all of the following criteria: |
| | • Increases dose on own (without physician's approval) |
| | • Never skips a dose |
| | • Never forgets to take a dose |
| 1 | Use for purposes other than intended |
| | If the subject answers yes to two or more of the following: |
| | • Takes more when upset |
| | • Takes more when discouraged |
| | • Makes subject feel intoxicated |
| | • Puts subject in good mood |
| 1 | Inability to stop use |
| | If the subject answers yes to at least one of the following: |
| | • Physician said to stop or cut down |
| | • Subject tried to stop and responded that it was somewhat or very hard |
| | • Did not try to stop but said it would be hard |
| 1 | Evidence of opioid withdrawal |
| | If the Withdrawal Score is 52 or more (range 24–120) |

*Data Quality*

Several routines were established to assure data integrity. A series of checking programs were run to check for any skips, errors, or inconsistencies in the data, and frequencies were checked before and after data corrections were made.

## Results

*Distribution of Subjects*

A total of 11,352 subjects were enrolled in this study. The sampling ratio within each arm was approximately three to one, suggesting that the randomization procedures were followed. Fig. 1 shows the target for each arm with the actual number of subjects in parentheses.

*Completed Interviews*

Nearly 72% ($n = 8139$) of the 11,352 subjects completed all nine interviews. A total of 87,180 interviews or 85% of all possible interviews (102,168) were completed.

A comparison of attrition by arm of study suggested that the completion rates were similar across the three arms of the study. Seventy percent (70.4%) of the subjects in the H-T arms compared to 72.1% in the tramadol arm, and 73.3% in the N-T arm completed all nine interviews.

*Sample Characteristics*

The population was primarily female (68.2%), which was consistent with the primary pain diagnoses of subjects entering the study. The sample was also primarily white (84%), over 36 years of age (86.8%), and over half (54%) were not employed (Table 2).

Up to three pain diagnoses were recorded for each patient using the International Classification of Diseases criteria (ICD-9-CM).[46] The following ICD diagnoses accounted for more than three-quarters of the primary diagnoses: osteoarthritis (19.9%), other disorders of the back (16.6%), other disorders of the soft tissue (10.0%), other/unspecified joint disorders (8.0%), rheumatoid arthritis (6.3%), and a variety of disc, knee, and cervical disorders (15.6%).

The mean pain scores at study entry were generally higher for the hydrocodone/tramadol arm (7.6), followed by the tramadol arm alone (7.3), and the NSAID/tramadol arm (6.9).

*Rate of Abuse*

The term "hit" was used to denote a positive score or case on the Abuse Index, e.g., two out of a possible three points if the Withdrawal Scale was not used or three out of a possible four points if the Withdrawal Scale was used. The hit rates for NSAIDs and tramadol were similar, while the rate for hydrocodone was higher (Table 3). There was no statistically significant difference between the rates for tramadol and NSAIDs. However, the rate for hydrocodone was significantly different than that of NSAIDs and tramadol ($P < 0.01$).

There were a total of 559 cases of a positive hit on the Abuse Index for the three reference medications. While each case within a specific reference medication represented a person, an individual counted as a hit on tramadol might have also been classified as a hit on NSAIDs. The 559 cases represented a total of 506 individuals, 102 of whom hit only on tramadol, compared to 176 who hit on only hydrocodone, and 177 who hit only on NSAIDs. The remaining 51 hit on multiple drugs.

The overall rates yield the highest prevalence estimate since there was no measure of

*Table 2*
**Sample Characteristics by Study Arm (Percent)**

| | ARM | | | |
|---|---|---|---|---|
| Characteristics | H-T ($n = 4321$) | N-T ($n = 5556$) | T ($n = 1475$) | Total ($N = 11{,}352$) |
| Gender | | | | |
| Male | 33.8 | 30.9 | 29.2 | 31.8 |
| Female | 66.2 | 69.1 | 70.8 | 68.2 |
| Race | | | | |
| White | 83.7 | 83.6 | 87.0 | 84.0 |
| Black | 13.1 | 13.4 | 9.3 | 12.7 |
| Asian/Pacific Islander | 0.3 | 0.4 | 0.6 | 0.4 |
| Native American | 1.1 | 1.0 | 1.6 | 1.1 |
| Other | 1.9 | 1.6 | 1.5 | 1.7 |
| Hispanic origin | | | | |
| Yes | 3.7 | 3.7 | 3.5 | 3.7 |
| No | 96.3 | 96.3 | 96.5 | 96.3 |
| Age (years) | | | | |
| 18–35 | 11.9 | 14.5 | 11.9 | 13.2 |
| 36–50 | 39.2 | 34.1 | 34.8 | 36.1 |
| 51–65 | 33.1 | 34.6 | 33.5 | 33.9 |
| 66+ | 15.7 | 16.8 | 19.8 | 16.8 |
| Selected primary diagnosis | | | | |
| Diffuse diseases of connective tissue | 2.0 | 1.9 | 1.4 | 1.9 |
| Rheumatoid arthritis | 5.9 | 6.7 | 5.8 | 6.3 |
| Osteoarthritis | 17.4 | 22.7 | 16.6 | 19.9 |
| Other arthropathies | 3.9 | 5.3 | 4.1 | 4.6 |
| Other unspecified joint disorders | 7.2 | 8.4 | 8.7 | 8.0 |
| Intervertebral disk disorders | 6.5 | 3.7 | 5.1 | 4.9 |
| Other unspecified disorders of back | 21.3 | 13.2 | 15.9 | 16.6 |
| Other disorders of soft tissue | 8.3 | 9.8 | 15.8 | 10.0 |
| Sprains and strains | 6.8 | 4.8 | 3.7 | 5.4 |
| Other | 20.7 | 23.5 | 22.9 | 22.4 |
| Mean pain score at baseline | 7.6 | 6.9 | 7.3 | |

persistence; a hit at one interview was all that was required. Table 3 also shows the effect of introducing a measure of persistence by requiring hits at two or more interviews (row 2). While these rates were substantially lower (NSAIDs 0.5%, tramadol 0.7%, and hydrocodone 1.2%), the conclusion was the same. That is, the relative abuse of hydrocodone was significantly higher than either tramadol or NSAIDs ($P < 0.01$).

One component of the algorithm, "use for purposes other than intended," actually contains two concepts "use for purposes other than intended" such as anxiety and depression and "good mood and feeling intoxicated." Since some patients might say that the medication put them in a good mood because it relieved their pain, all cases in which good mood and feeling intoxicated were the only components measured on this criterion were removed and the prevalence rates recalculated. The resulting prevalence rates were hydrocodone 2.24%, tramadol 1.07% ($P < 0.01$), and NSAIDs 1.06% ($P < 0.01$).

### Prior Drug History

Of the 11,352 subjects, 128 were recorded as having a previous history of drug abuse, 9275

*Table 3*
**Distribution of Positive Cases by Continuity of Hits for Hydrocodone, Tramadol, and NSAIDs[a]**

| | Hydrocodone $n = 4278$ | | Tramadol $n = 4965$ | | NSAID $n = 8589$ | |
|---|---|---|---|---|---|---|
| | Frequency | % | Frequency | % | Frequency | % |
| 1 hit | 159 | 3.7 | 97 | 2.0 | 176 | 2.0 |
| 2 or more hits | 49 | 1.2 | 36 | 0.7 | 42 | 0.5 |
| Total | 208 | 4.9 | 133 | 2.7 | 218 | 2.5 |

[a]Percentages based upon total population exposed to medication.

did not have a history of drug abuse, and history was unknown in 1949 subjects. Of the 506 individuals who had a positive hit on the Abuse Index for one or more of the three reference medications, seven individuals had a known history of drug abuse, 407 had no history of drug abuse, and in 92 cases the history was unknown. The resulting rates were 5.5% for those with a prior history of abuse, 4.4% for those with no prior history, and 4.7% where the history was unknown. There is no significant difference among these groups.

### Characteristics of Abusers

No significant differences were found in the distribution by gender, age, or employment status across type of medication to which subjects were exposed. There were some differences between characteristics at admission and those who met the criteria for abuse. Across all three drugs, those who met the criteria were more likely to be between the ages of 36 and 50 years and to report that they were not employed due to a disability.

The duration of exposure to hydrocodone, tramadol, and NSAIDs varied depending on whether the subject met the criteria specified in the algorithm. Mean exposure for those not meeting the criteria was 17 weeks for hydrocodone, 18 weeks for tramadol, and 24 weeks for NsAIDs, compared to 28, 30, and 31 weeks, respectively for those meeting the criteria. In addition, approximately half of those subjects initially assigned to NSAIDs remained on NSAIDs (53.3%) compared to about one-third of those randomized to hydrocodone (33%) or tramadol (33.7%).

Bodily Pain scores from the SF-36 improved for all subjects, while "average pain this week" measured on the 0–10 scale showed significant improvement for those patients not classified as hits and for patients taking hydrocodone who were classified as hits. In contrast to the Bodily Pain scores noted above, where improvements were seen across the board, improvements in average weekly pain for tramadol and NSAID patients classified as hits were not significant.

Thirty percent of all subjects smoked and 50% drank. Among cases, 41.5% smoked compared to 29.6% among noncases ($P < 0.01$). While equal proportions of cases and noncases drank, 14.4% of cases were classified as heavy drinkers compared to 9.7% of noncases ($P < 0.01$).

## Discussion

The results of this study suggest that the rate of abuse/dependence in a chronic pain population that was primarily female and over the age of 36 ranged from 2.5% to 4.9% based on a single hit and from 0.5% to 1.2% if a measure of persistence (two or more hits) was used. The prevalence rates for NSAIDs and tramadol were significantly less than the rate for hydrocodone-containing analgesics.

As noted previously, hydrocodone was included as a positive comparator and NSAIDs as the negative. While hydrocodone is known to be abused, little is known about the abuse of NSAIDs. In a sense, it was included as a placebo vis-à-vis abuse. A review of the literature suggests that some abuse or misuse of these products occurs, as exhibited by overuse headaches and hypokalemia.[47,48] However, we are not aware of any studies of NSAID abuse using addiction-related criteria.

The pain scores suggest that subjects suffered from moderate-to-severe pain, and that the subjects were generally assigned to groups as would be expected according to the World Health Organization guidelines for cancer pain. That is, the mean pain score for subjects assigned to the hydrocodone vs. tramadol arm was higher than for tramadol alone, which was higher than the pain score for those in the NSAIDs vs. tramadol arm.

Within each arm, at least 70% of the subjects completed all nine interviews during the 12-month period, and between 75% and 79% completed the eight interviews within 9 months. Attrition rates were similar for all arms of the study. These represent relatively low attrition rates for a 12-month study in which subjects paid for their medication.

Consideration was given to analyzing only those subjects who completed all nine interviews, but if the attrition was higher among cases, then the prevalence rates would have been artificially low. For example, in one study, the rate would have dropped from almost 28% to 5% if the analysis was based on only those patients in treatment at one year (18). Thus, the decision was made to analyze all subjects, including those who dropped out early.

Previous studies have attempted to measure abuse and dependence in various patient populations. These studies have used widely disparate criteria to measure abuse or dependence.[20,49,50] The criteria included in this study were consistent with the model of four distinguishable but overlapping features of chronic pain, including medication usage, physical functioning, emotional functioning, and pain intensity.[30] Although developed in 1994, the domains included in the questionnaire were also consistent with several of the measures suggested in the more recent consensus statement entitled "Definitions Related to the Use of Opioids for the Treatment of Pain" and others.[27,33,34] The key measures in the algorithm were 1) increase in dose on own without physician's approval; 2) use of analgesics for other symptoms such as anxiety, depression, or use for intoxication; 3) difficulty stopping, for reasons other than return of pain, including physician said to stop using; and 4) withdrawal. Past history of addiction, smoking history, and alcohol use were also collected. Consistent with the literature, cases were more likely to be current smokers and heavy drinkers.[35–38]

This approach of using multiple measures recognized as being associated with addiction is considered one of the strengths of this study. Relying on a single indicator or such measures as "feeling addicted" is likely to yield less reliable, but higher rates of abuse than an approach requiring a constellation of behaviors. For example, in one study of pain outcomes, approximately 40% of patients expressed at least one aberrant behavior.[51] Although the rate of abuse and dependence among those using hydrocodone-containing analgesics was 4.9%, almost 30% (28.45%) exhibited at least one of the behaviors included in the index.

With regard to those subjects who were counted as a hit because they said that the drug put them in a good mood, it is certainly plausible that a subject responded that he or she was in a good mood because his or her pain was relieved. Removal of the cases in which "good mood and feeling intoxicated" were the only components of this segment of the algorithm and including only those cases where there was "use for purposes other than intended" yielded prevalence rates ranging from 1.06% and 1.07% for NSAIDs and

tramadol to 2.2% for hydrocodone-containing analgesics. Future studies will separate these components and probe on positive responses. The general improvement in pain scores suggests that "increasing the dose without physician approval" was likely a measure of abuse/dependence, not pseudoaddiction.[52]

The National Household Survey on Drug Abuse (NHSDA) collects data on the nonmedical use of drugs and uses DSM-IV criteria to estimate abuse and dependence. The 2000 NHSDA data suggest that among nonmedical users of pain relievers, the rate of dependence is approximately 7% among those aged 26 and older. Given that this is a rate among those who engage in nonmedical use of pain relievers, our estimates of abuse and dependence seem reasonable. Furthermore, in Fishbain et al.'s review, the three studies that attempted to address the concepts of psychological dependence and compulsive use found rates of 5.3%, 3.2%, and 16%.[53–55] The assessment in the latter study was based upon clinical judgment without defined criteria. A more recent study found an addiction rate of 2.8% in CNP patients.[56]

This study had several strengths: 1) it was conducted as a prospective study thereby providing incidence rates; 2) there was random assignment within the NSAIDs and hydrocodone treatment arms; 3) since after the initial random assignment the study was conducted as a natural history study, it had the advantage of reflecting behaviors occurring under real world conditions; 4) it was sufficiently powered to detect even low levels of abuse/dependence; 5) both positive and negative controls were used; 6) it used a standardized questionnaire that was based upon the experience of several experts, was consistent with the current literature and a consensus statement released several years after the questionnaire was developed[27]; 7) an algorithm was developed a priori to estimate abuse/dependence based upon multiple indicators rather than relying on a single indicator (the primary components of the algorithm are recognized as measures of addiction); 8) providing an estimate based on a single hit rather than two or more hits was a more conservative approach; and 9) a dedicated team of experienced and well trained interviewers administered the more than 87,000 interviews with subjects who were followed for up to 12 months.

One potential criticism is that by excluding patients with active substance abuse problems, we would be unlikely to find very much. This, of course, was the point. Our overall hypothesis was that abuse/dependence in patient populations was low and that for tramadol it would be very low. We did allow patients with a past history of abuse in the study. It is unclear how well primary care practitioners, rheumatologists, and orthopedists screen for histories of substance abuse, and therefore the number of subjects with a past history of abuse could have been underestimated. However, the rate of abuse in subjects with a known history of abuse was similar to those without a history of abuse (4.4%–5.5%). It may be that since their drug abuse history was known, these subjects were more carefully monitored. Nonetheless, these data do seem to support the contention that patients with histories of drug abuse can safely be treated with tramadol or hydrocodone-containing analgesics. One can only speculate what would have happened if current substance abusers were not excluded from the study. It may be that they would have been closely monitored and the rates of abuse would be similar to former abusers. It is also possible that they may have abused tramadol in addition to whatever they were already abusing, or transferred their abuse to tramadol. Based upon previous studies in high-risk populations, these latter alternatives seem less likely.[14,15]

Another potential limitation of the study was that although the questionnaire was based on existing literature and expert consultation, no independent clinical assessment of individual cases was done. In retrospect, in the initial phases of the study, we could have had a physician experienced in addiction medicine interview subjects who appeared to be abusing their medication to help validate the algorithm. This approach was used successfully in a study of the nicotine inhaler and we plan to include this approach in future studies.[57]

Another potential criticism is that the algorithm did not capture all the elements necessary to produce an estimate of abuse or dependence. The algorithm did include several measures that are recognized as measures of abuse or dependence. The patients had to have increased their dose without their physician's approval, taken their medication for

purposes other than pain relief and/or reported that they could not stop for a reason that was not related to the relief of pain. However, the latest version has been updated to include additional measures, such as personal problems and methods of obtaining medications.

## Conclusions

These results support the hypothesis that the rate of abuse identified with tramadol is not significantly greater than NSAIDs, but is less than the rate associated with hydrocodone. Furthermore, abuse/dependence in this population was low overall and consistent with other studies of large patient populations. Importantly, the rate was also relatively low among chronic pain patients with a history of drug abuse. Considering that two recent studies of more than 1000 patients each indicated that less than 25% of patients felt that their pain was adequately controlled,[58,59] we hope that these results will help allay fears about patients becoming addicted, contribute to the appropriate treatment of pain, and help improve the measurement of abuse/dependence/addiction in patient populations.

## References

1. Villarreal JE, Seevers MH. Evaluation of new compounds for morphine-like physical dependence in the rhesus monkey. Proceedings of the National Academy of Sciences-National Research Council Committee on Problems of Drug Dependence 30th meeting, National Academy of Sciences, 1968, pp. 1–15.

2. Friderichs VE, Felgenhauer F, Jongschaap P, Osterloh G. Pharmakologische untersuchungen zur analgesie, abhängigkeits-und toleranzentwicklung von tramadol, einem stark wirkenden analgetikum (Pharmacological investigations on analgesia and the development of dependence and tolerance with Tramadol, a strongly acting analgesia). Arzneimittelforschung 1978;28:122–134.

3. Murano T, Yamamoto H, Endo N, et al. Studies of dependence on tramadol in rats. Arzneimittelforschung 1978;28:152–158.

4. Yanagita T. Drug dependence potential of 1-(m-methoxyphenyl)-2-dimethylaminomethyl)-cyclo-hexan-1-ol hydrochloride (tramadol) tested in monkeys. Arzneimittelforschung 1978;28:158–163.

5. Arend VI, von Arnim B, Nijssen J, Scheele J, Flohe L. Tramadol and pentazocine in a clinical double-blind crossover comparison. Arzneimittelforschung 1978;28:199–208 [in German].

6. Richter W, Giertz H. Clinical evaluation of dependence-liability of tramadol. Naunyn Schmiedebergs Arch Pharmacol 1980;313(suppl): R62. [abstract].

7. Preston KL, Jasinski DR, Testa M. Abuse potential and pharmacological comparison of tramadol and morphine. Drug Alcohol Depend 1991;27:7–17.

8. Keup W. Missbrauchsmuster Bei Abhangigkeit Von Alcohol, Medikamenten Und Drogen: Fruhrwarnsystem-Daten Fur Dei Bundesrepublik Duetschland 1976–1990 (Rates of dependence on alcohol, medications, and drugs in the early warning system in Germany:1976–1990). Freiburg im Breisgau: Lambertus, 1993.

9. Food and Drug Administration. Minutes of the FDA Drug Abuse Advisory Committee #27, 1994.

10. Sigler KA, Guernsey BG, Ingrim NB, et al. Effect of a triplicate prescription law on prescribing of schedule II drugs. Am J Hosp Pharm 1984;41: 108–111.

11. Weissman DE, Joranson DE, Hopwood MB. Wisconsin physicians' knowledge and attitudes about opioid analgesic regulations. Wis Med J 1991;90: 671–675.

12. Joranson DE, Cleeland CS, Weissman DE, Gilson AM. Opioids for chronic cancer and non–cancer pain: a survey of state medical board members. Fed Bull 1992;79:15–49.

13. Joranson DE, Gilson A. Controlled substances, medical practice, and the law. In: Schwartz HI, ed. Psychiatric practice under fire: The influence of government, the media and special interests on somatic therapies, 1st ed. Washington, DC: American Psychiatric Press, 1994: 173–194.

14. Cicero TJ, Adams EH, Geller A, et al. A postmarketing surveillance program to monitor Ultram® (tramadol hydrochloride) abuse in the United States. Drug Alcohol Depend 1999;57:7–22.

15. Knisely JS, Campbell ED, Dawson KS, Schnoll SH. Tramadol post-marketing surveillance in health care professionals. Drug Alcohol Depend 2002;68:15–22.

16. Porter J, Jick H. Addiction rare in patients treated with narcotics. N Engl J Med 1980;302:123. [letter].

17. Perry S, Heidrich G. Management of pain during debridement: a survey of U.S. burn units. Pain 1982;13:267–280.

18. Chabal C, Erjavec MK, Jacobson L, Mariano A, Chaney E. Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors. Clin J Pain 1997;13:150–155.

19. Zenz M, Strumpf M, Tryba M. Long-term oral opioid therapy in patients with chronic nonmalignant pain. J Pain Symptom Manage 1992;7:69–77.

20. Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. Clin J Pain 1992;8:77–85.

21. Spitzer RL, Williams JB, Gibbon M, First MB. The structured clinical interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry 1992;49(8):624–629.

22. Robins LN, Wing J, Wittchen HU, et al. The composite international diagnostic interview. An epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry 1988; 45(12):1069–1077.

23. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: American Psychiatric Association, 2000. Text revision.

24. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 3rd ed. Washington, DC: American Psychiatric Association, 1987. Revised.

25. Aronoff GM. Opioids in chronic pain management: is there a significant risk of addiction. Curr Rev Pain 2000;4:12–21.

26. Sees KL, Clark HW. Opioid use in the treatment of chronic pain: assessment of addiction. J Pain Symptom Manage 1993;8:257–264.

27. Savage S, Covington EC, Heit HA, et al. Definitions related to the use of opioids for the treatment of pain: a consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine. Available from. www.ampainsoc.org/advocacy/opioids2.htm. Accessed April 27, 2006.

28. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Emergency department trends from the drug abuse warning network, final estimates 1995–2002, DAWN Series: D-24, DHHS Publication No. (SMA) 03-3780, Rockville, MD, 2003.

29. Drug Enforcement Administration, Office of Diversion Control. National Forensic Laboratory Information System. Annual report, 2002.

30. De Gagne TA, Mikail SF, D'Eon JL. Confirmatory factor analysis of a 4-factor model of chronic pain evaluation. Pain 1995;60:195–202.

31. Tait RC, Chibnall JT, Duckro PN, Deshields TL. Stable factors in chronic pain. Clin J Pain 1989;5: 323–328.

32. Flor H, Turk DC. Chronic back pain and rheumatoid arthritis: predicting pain and disability from cognitive variables. J Behav Med 1988;11: 251–265.

33. Portenoy RK. Opioid therapy for chronic non-malignant pain: current status. In: Fields HL, Liebeskind JC, eds. Pharmacological approaches to the treatment of chronic pain: New concepts and critical issues. Seattle, WA: IASP Press, 1994: 247–287.

34. Compton P, Darakjian J, Miotto K. Screening for addiction in patients with chronic pain and "problematic" substance use: evaluation of a pilot assessment tool. J Pain Symptom Manage 1998;16: 355–363.

35. Stark MJ, Campbell BK. Drug use and cigarette smoking in applicants for drug abuse treatment. J Subst Abuse 1993;5(2):175–181.

36. Degenhardt L, Hall W. The relationship between tobacco use, substance-use disorders and mental health: results from the National Survey of Mental Health and Well Being. Nicotine Tob Res 2001;3(3):225–234.

37. Burns L, Teesson M. Alcohol use disorders comorbid with anxiety, depression and drug use disorders. Findings from the Australian National Surrey pf Mental Health and Well Being. Drug Alcohol Depend 2002;68(3):299–307.

38. McColl RM, Pascal Richter K. Why do so many drug users smoke? J Subst Abuse Treat 2003;25(1): 43–49.

39. Babor TF, Grant M. From clinical research to secondary prevention: International collaboration in the development of the alcohol use disorders identification test (AUDIT). Alcohol Health Res World 1989;13:371–374.

40. Public Law 91–513, H.R. 18583. Title II. Section 101.1, October 27, 1970.

41. Minutes of the Drug Abuse Advisory Committee, April 1998. Food and Drug Administration. http://www.fda.gov/ohrms/dockets/ac/98/transcript/3411t2.rtf. Accessed 1/21/2005.

42. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain 1983;17(2):197–210.

43. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-item short-form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247–263.

44. Ware JE, Kosinski M, Keller SD. SF-36 physical & mental health summary scales: A user's manual, 5th ed. Boston, MA: Health Assessment Lab, 1994.

45. Ware JE Jr, Snow KK, Kosinski M, Gandek B. SF-36 health survey: manual and interpretation guide, 2nd ed. Boston, MA: Health Institute, 1993.

46. International classification of diseases, Ninth revision, clinical modification, 5th ed. Practice Management Information Corporation, Los Angeles, CA. 1998.

47. Fritsche G, Diener HC. Medication overuse headache—what is new? Expert Opin Drug Saf 2002;1(4):331–338.

48. Dyer BT, Martin JL, Mitchell JL, Sauven NC, Gazzard B. Hypokalemia in ibuprofen and codeine phosphate abuse. Int J Clin Pract 2004;58(11): 1061–1062.

49. Kouyanou K, Pither CE, Rabe-Hesketh S, Wessely S. A comparative study of iatrogenesis, medication abuse, and psychiatric morbidity in chronic pain patients with and without medically explained symptoms. Pain 1998;76:417–426.

50. Maruta T, Swanson DW, Finlayson RE. Drug abuse and dependency in patients with chronic pain. Mayo Clin Proc 1979;54:241–244.

51. Passik SD, Schein JR, Dodd SL, et al. A new tool to assess and document pain outcomes in chronic pain patients receiving opioid therapy. The 6th International Conference on Pain and Chemical Dependency. New York, NY, February 5–7, 2004.

52. Weissman DE, Haddox JD. Opioid pseudoaddiction: an iatrogenic syndrome. Pain 1989;36:363.

53. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. Pain 1986;25:171–186.

54. Medina JL, Diamond S. Drug dependency in patients with chronic headache. Headache 1977;17: 12–24.

55. Evans PJD. Narcotic addiction in patients with chronic pain. Anaesthesia 1981;36:597–602.

56. Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG. A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Med 2003;4(4):340–351.

57. Hughes JR, Adams EH, Franzon MA, Maguire MK, Guary J. A prospective study of off-label use of, abuse of, and dependence on nicotine inhaler. Tob Control 2005;14(1):49–54.

58. Adams EH, Shaikh S, Haddox JD, Schnoll SH. Self-reported efficacy and adherence associated with modified-release opioids. CPDD Annual Meeting. June, 2004.

59. Guary J, Adams EH, Haddox JD, Schnoll SH. Patient Perceptions of Addiction. CPDD Annual Meeting. June, 2004.