Abstract
The objective of this study was to describe pain tolerance in drug abusers. Research suggests that drug dependence and pain perception share common neuroanatomical and neurophysiological substrates; thus the abuse of psychoactive drugs was hypothesized to relate to pain tolerance. We examined cold-pressor pain tolerance in 122 male, current and former opioid and cocaine abusers, across use status and primary drug of abuse. Descriptive analyses showed that the ratio of pain-sensitive to pain-tolerant persons was considerably higher than that described in the normative cold-pressor pain literature. Two-way analysis of variance revealed a significant main effect for using status, indicating that current drug use is associated with decreased pain tolerance. The main effect for drug type approached significance, implying that persons who abuse opioids manifest less pain tolerance than cocaine users. The findings emphasize the importance of studying pain tolerance and drug abuse as interrelated phenomena. J Pain Symptom Manage 1994;9:462-473.

Key Words
Cold-pressor test, pain tolerance, opioid abuse, cocaine abuse, methadone maintenance

Introduction
The management of pain in the population of patients with a drug-abuse history poses several challenging clinical problems. Obtaining a reliable drug use history may be difficult, treatment philosophies pertaining to the use of analgesic drugs frequently conflict, and moralizing by and/or lack of knowledge on the part of the staff about the nature and course of drug abuse is common.1-5 Although overlap between brain systems responsible for both pain and drug dependence is increasingly appreciated, there is a general lack of knowledge about pain perception in patients known to be past or current abusers of psychoactive drugs. The objective of this research was to develop a better understanding of pain tolerance among drug abusers and to explore drug abuse variables that may affect pain tolerance. Such information should ultimately improve the management of pain in this group.

Evidence exists to suggest that certain drug abusers have decreased pain tolerance when compared to drug-naive persons. Ho and Dole6 and Martin and Inglis7 demonstrated de-
creased pain tolerance to cold-pressor trials in both methadone-maintained and abstinent opioid addicts when compared with normals. These studies, however, were limited by small sample sizes, incomplete drug histories, and lack of verification of dependence for drug-abusing subjects, as well as the methodological problem of prematurely ending cold-pressor trials before absolute level of pain tolerance could be established.

Pain perception and drug abuse have been linked in less direct ways. For example, hyperalgesia, or oversensitivity to noxious stimuli, is a clinical finding of the opioid withdrawal syndrome. Personality studies reveal that opioid and amphetamine abusers have elevated hypochondriasis scores on the Minnesota Multiphasic Personality Inventory, indicative of increased self-concern and narcissism. These scores, however, approach normal levels with abstinence, prompting Martin and colleagues to describe as a salient characteristic of the addict, "a proneness to overreact or be overly concerned about discomfort." Thus, hypochondriasis, possibly induced by drug abuse, could manifest as decreased pain tolerance.

Accumulating knowledge of the mechanisms underlying pain and drug dependence suggest that drug abuse and pain perception are related phenomena. Recent convergent conceptualizations of the neuroanatomy and neurophysiology of pain and drug dependence suggest that abusers of many types of psychoactive drugs might evidence altered pain tolerance via changes in the descending pain-control pathways that originate in midbrain systems, pathways that are also implicated in the reinforcing effects of addictive drugs. Most drugs of abuse activate the mesolimbic dopamine pathway, which runs between the ventral tegmental area (VTA) and the nucleus accumbens and produces subjective reward. Such brain-mediated mechanisms are theorized to be responsible for the reinforcing effects of psychoactive drugs. Stimulation of the VTA also produces analgesia. When this brain area is electrically stimulated, it activates opioid and nonopioid systems that decrease pain perception.

In the aggregate, these findings suggest that overlap exists between the midbrain structures which, when electrically stimulated, produce both reward and analgesia. Furthermore, the effects of such stimulation, which are reinforcing in animals, are reversible with the opioid antagonist naloxone. This finding implies that there is involvement of the endogenous opioid system in the effects produced by most drugs of abuse. Hence, although reward and analgesia are demonstrated to be distinct processes, many psychoactive drugs activate their shared anatomical basis.

Further, many of the same opioid and nonopioid neurotransmitters/neuromodulators are involved in the perception of both pain and reward. Several of the so-called "first-stage" neurochemical systems directly affected by psychoactive drug ingestion [specifically, γ-aminobutyric acid (GABA), norepinephrine, serotonin and the opioid peptides], and which precede "second-stage" dopamine release, are substances that could affect pain tolerance via both opioid- and non-opioid-mediated descending pathways. Thus, neurotransmitters implicated in both drug dependence and pain perception further link these two phenomena.

The temporal nature of the link between pain tolerance and drug use is not clear. Brain-mediated or descending pain-control systems, which modulate incoming pain signals and the conscious perception of pain, may undergo adaptive changes secondary to drug abuse and manifest as altered pain tolerance. Alternatively, neurophysiologic aberrations that affect pain tolerance and predate drug use behavior cannot be ruled out. The self-medication model of drug abuse, for example, posits that persons use drugs to counteract or correct underlying dysphoric psychological or personality characteristics that are believed to be rooted in preexisting neurophysiologic abnormalities. Several researchers have provided evidence that these neurophysiologic traits may be at least in part genetic in origin, predisposing certain individuals to problematic drug use. Thus, individual variations in pain tolerance may partially be explained by genetic differences in neurotransmitter systems implicated in both pain tolerance and drug abuse.

Further complicating the relationship between drug abuse and pain tolerance are the analgesic effects of opioids. Midbrain-mediated modulation of pain perception co-occurring with the abuse of psychoactive drugs may supplement or alter opioid-mediated analges-
Evidence that opioid-specific effects on pain perception would be distinct from those mediated by other drugs of abuse is presented by Wise and Bozarth, who point out that the sites for physical dependence and tolerance to specific drug effects are individual to each drug abuser, and are separate from the mesolimbic reward system. Evidence for the dissociation of opioid physical dependence and reward is provided by the finding that physical tolerance does not develop when opioids are infused directly into the brain reward system.

Thus, opioid abusers, in contrast with abusers of other psychoactive drugs, are suspected of having unique changes in pain tolerance. Endogenous opioid-mediated pain-control systems may specifically be altered by the analgesic and tolerance-producing characteristics of the drugs they preferentially abuse. Although not proved, the presence of chronic exogenous opioids may allow cross-tolerance to develop to endogenous opioid system activity, thereby decreasing pain tolerance. However, researchers, using a variety of methods, have not been able to demonstrate change in receptor number or sensitivity in opioid addicts, nor in endogenous opioid levels in the cerebrospinal fluid and blood of stable methadone and buprenorphine-maintained individuals. Although not fully understood, changes within or specific to the endogenous opioid system may partially explain alterations in pain tolerance specific to opioid abusers.

To clarify these observations, the present study describes pain tolerance to a standardized acute pain stimulus, the cold-pressor test (CPT), in persons with a history of drug abuse. The purpose of this study was to validate and expand upon clinical evidence of decreased pain tolerance in known drug abusers in two ways. First, pain tolerance in drug abusers currently using drugs was compared with pain tolerance in abstinent drug abusers. If constant across drug-using states, some support is provided for genetic or trait explanations for drug abuse and pain tolerance, whereas if cold-pressor pain tolerance changes with use status, neuroadaptation to drug abuse, manifest in pain perception, is suspected. Second, abusers of two different types of drugs (cocaine and opioids) were compared to learn if pain tolerance is similar across these two common drugs of abuse. If so, this would imply general reward-system adaptation to drug dependence, rather than processes that specifically relate to opioid-mediated analgesia or tolerance.

**Method and Procedures**

**Design and Sample**

The study was quasi-experimental with subjects blocked by preexisting characteristics (that is, primary opioid vs cocaine abusing history; and abstinent vs current drug-using status). Preexisting normative data on human CPT pain tolerance were available for comparison with this sample.

A total of 122 treatment-seeking drug abusers who met DSM-III-R criteria for a substance dependence disorder were studied. This number of subjects was calculated to provide a statistical power of 0.96, assuming a one-tailed test, an effect size of 0.30, and an \( \alpha \) of 0.05. Subjects were recruited in a medium-sized Northeast city (approximate population, 100,000) from a large nonprofit addiction-treatment foundation that provides both inpatient and outpatient drug treatment services, as well as rehabilitative and follow-up services to former users.

Men between the ages of 25 and 45 years with a history of cocaine and opioid abuse were asked to participate in the study. Women were excluded, as pain tolerance is known to vary with menstrual cycle phase. Additionally, persons reporting a history of conditions known to affect pain tolerance (for example, peripheral neuropathy, depression, and schizophrenia) were excluded.

**Measures**

The acute monophasic pain stimulus was provided by a standard CPT. An ice bath maintained at 0–2°C was prepared. Tolerance was measured by how many seconds the subject could keep his dominant hand and forearm immersed in the ice bath before immersion became subjectively unbearable. Although affective components to cold-pressor elicited pain are present, the excellent reproducibility of CPT pain patterns across individuals and environments, and the reliable effect of opioid
and nonopioid analgesic challenges on CPT performance demonstrate that the CPT response clearly reflects the sensory dimension of pain. To minimize the effects of social desirability on performance, instructions were given that provided a socially acceptable reason, as described by Kohn and colleagues, to remove the hand from the bath. All trials were truncated at 5 min, as cold-pressor pain has been shown to peak at 60–90 sec and subside below tolerance threshold within 4–5 min of immersion.

Subject responses to a structured interview, the Addiction Severity Index (ASI), provided information on the type of drug for which subjects had sought treatment (either cocaine or opioid), as well as demographic, health, social, and drug history information. The ASI is a widely used drug-abuse treatment and research assessment tool with documented reliability and validity.

The ASI also provided information on whether or not the subject was currently drug free or continued to use a form of his identified problem drug. Subjects were considered abstinent if they had been drug free for at least 6 weeks, with the exception of moderate alcohol and marijuana use, during which time the acute effects of withdrawal for both street opioids and cocaine should have subsided. All opioid addicts classified as drug using were methadone-maintained as a part of treatment.

**Procedure**

Approval for the study was received from the addiction-treatment foundation. Potential participants were recruited via announcements in client group meetings or posters hung in treatment facilities. All recruitment materials stressed that subjects could not participate when acutely intoxicated, and the Rapid Eye Test was administered immediately before testing to screen for intoxication. Via informed consent procedures, all subjects were assured that the single CPT was time limited and safe. All methadone-maintained persons received their methadone dose at the usual time, and the elapsed time between methadone ingestion and testing was noted. Participation in the study was voluntary and confidential, and subjects were paid for their time.

**Results**

Table 1 provides demographic information on all subjects. Average subject age was 33.6 years with an average of 10 years of regular drug use. The ethnic composition was 50% non-Hispanic white, 36.1% African-American, and 13.9% Hispanic. As expected, polydrug use was evident in all four groups of drug abusers (Figure 1). Of methadone-maintained (current opioid) subjects, 43% reported cocaine use in the past 30 days (mean of 9 days of use), while current cocaine users reported no opioid use. Of those on methadone, 16% reported only treatment methadone use.

Figure 2 presents pain tolerance (measured in seconds) to the CPT for all subjects, differentiated by drug type and using status. For the entire sample, pain tolerance ranged from 10.7 to 300 sec (mean, 106 sec; SD, 102 sec). Pain tolerance scores were bimodally distributed, with the first mode occurring at 32 sec (describing a relatively pain-sensitive group), and the second at 300 sec (describing a more pain-tolerant group). Average immersion times ranged from 65 sec for current opioid users to 167 sec for abstinent cocaine users. Pain tolerance for those subjects maintained on methadone who reported cocaine use in the past 30 days (N = 18) fell between those currently using methadone and cocaine (mean, 70.5 sec; SD, 87.4 sec).

Average cold-pressor pain tolerance for this sample does not appear to differ from that found for a normative sample of men between the ages of 20 and 50 years (N = 177 years), who tolerated cold-pressor pain administered under similar conditions for an average of 86.1 sec (SD = 84.3 sec). However, the high percentage of past and current drug abusers who were pain intolerant was unanticipated. In their meta-analysis of six large CPT studies of men between the ages of 17 and 40 years (total N = 205), Chen and colleagues found the ratio of pain-sensitive to pain-tolerant subjects to be 1:14, whereas, in this sample, it was 5.4:1, using the same pain-tolerance cutoff criteria (180 sec) (Figure 3). Laboratory and experimental conditions utilized to produce the Chen and colleagues data were comparable to those utilized in the present protocol; both forearm and hand were plunged into a 1.0°C ± 0.3°C ice bath with palm placed flat on
Table 1
Sample Demographics

<table>
<thead>
<tr>
<th></th>
<th>Abstinent&lt;sup&gt;a&lt;/sup&gt; opiate users (N = 26)</th>
<th>Current&lt;sup&gt;b&lt;/sup&gt; opiate users (N = 43)</th>
<th>Abstinent&lt;sup&gt;a&lt;/sup&gt; cocaine users (N = 32)</th>
<th>Current&lt;sup&gt;b&lt;/sup&gt; cocaine users (N = 21)</th>
<th>Test statistics and P level&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Total sample (N = 122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>57.7%</td>
<td>67.4%</td>
<td>43.8%</td>
<td>14.3%</td>
<td>( \chi^2(6) = 27.4 ) P &lt; 0.000</td>
<td>50.0%</td>
</tr>
<tr>
<td>Black</td>
<td>23.1%</td>
<td>23.3%</td>
<td>34.4%</td>
<td>81.0%</td>
<td></td>
<td>36.1%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>19.2%</td>
<td>9.3%</td>
<td>21.9%</td>
<td>4.3%</td>
<td></td>
<td>13.9%</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (range, 25–45 years)</td>
<td>33.7 (5.7)</td>
<td>35.1 (4.8)</td>
<td>31.9 (6.0)</td>
<td>33.1 (5.1)</td>
<td>( F (3,118) = 2.2 ) P = 0.10</td>
<td>33.6 (5.5)</td>
</tr>
<tr>
<td>Education (range, 10–18 years)</td>
<td>12.0 (1.6)</td>
<td>11.7 (1.5)</td>
<td>12.4 (2.3)</td>
<td>11.9 (1.7)</td>
<td>( F (3,118) = 0.8 ) P = 0.51</td>
<td>12.0 (1.8)</td>
</tr>
<tr>
<td>Years of regular drug abuse (range, 0–6)</td>
<td>10.7 (7.2)</td>
<td>11.9 (8.7)</td>
<td>9.5 (7.2)</td>
<td>7.3 (5.9)</td>
<td>( F (3,118) = 1.9 ) P = 0.14</td>
<td>10.2 (7.6)</td>
</tr>
<tr>
<td>Number of drug treatment episodes (range, 0–20)</td>
<td>5.0 (5.0)</td>
<td>5.8 (5.4)</td>
<td>3.5 (3.8)</td>
<td>1.5 (1.5)</td>
<td>( F (3,118) = 4.9 ) P &lt; 0.01</td>
<td>4.3 (4.7)</td>
</tr>
<tr>
<td>Number of weeks drug free (range, 6–528)</td>
<td>59.2 (102.6)</td>
<td>—</td>
<td>39.3 (32.6)</td>
<td>—</td>
<td>( t(29.1) = 0.9 ) P = 0.35</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup>No self-reported use of problem substance for at least 6 weeks.

<sup>b</sup>Active methadone maintenance clients who may or may not have been using other substances.

<sup>c</sup>Testing for differences among subsamples.

Bottom of bath, and trials were truncated at 5 min.

Pain intolerance significantly correlated with using status (\( r = -0.37, P < 0.001 \)), such that persons currently using opioids or cocaine were significantly less pain tolerant (mean, 69.9 sec; SD, 74.8 sec) than those who were abstinent (mean, 144.8 sec; SD, 114.1; \( t, 4.24; P < 0.000 \)). Additional point-biserial correlation analysis between pain tolerance and drug type was also significant (\( r = 0.24, P < 0.01 \)), with current and abistent opioid abusers less tolerant of cold-pressor pain than current and abistent cocaine abusers.

Fig. 1. Polysubstance abuse in past 30 days in subjects (N = 122) by drug type and use status.
To eliminate potential confounding effects of extraneous variables, correlational analyses demonstrated that pain tolerance was not significantly related to room temperature or time of day. Because CPT pain tolerance has been demonstrated to vary by race, a one-way analysis of variance of race by pain tolerance time was conducted, revealing that pain tolerance was not significantly related to ethnic background in this sample \(F(2,119) = 0.6834, P = 0.51\). Number of previous treatment episodes did not correlate significantly with immersion time \(r = -0.04\). For those subjects maintained on methadone (average methadone dose was 66 mg/day; SD, 17 mg), pain tolerance did not significantly vary with time since methadone ingestion. Counterintuitively, cold-pressor pain tolerance decreased as methadone dose increased \(r = -0.25, P = 0.05\). For abstinent subjects, pain tolerance did not correlate with length of time drug free.

Pain tolerance of subjects based on drug type and using status was compared using a two-way analysis of variance (ANOVA) (Table 2). No significant interaction effect was found on pain tolerance between using status and problem drug \(F(1,118) = 0.961\). The main effect for drug type approached statistical significance \(F(1,118 = 3.522), P = 0.06\), and the main effect of using status was highly significant \(F(1,118 = 14.697), P < 0.001\). These same relationships among independent variables were demonstrated when ANOVA analyses were completed separately on white and nonwhite groups of subjects.

As using status appeared to play an important role in cold-pressor pain tolerance, drug-free and drug-using subjects were compared on demographic and addiction-history variables to explore alternative explanations for differences in pain tolerance. Variables tested included those believed to affect treatment
Table 2
Pain Tolerance by Drug Type and Using Status
(ANOVA)

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>df</th>
<th>Mean squares</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug type</td>
<td>1</td>
<td>31475.062</td>
<td>3.522a</td>
</tr>
<tr>
<td>Using status</td>
<td>1</td>
<td>131324.215</td>
<td>14.697b</td>
</tr>
<tr>
<td>Drug type x using</td>
<td>1</td>
<td>8590.757</td>
<td>0.961</td>
</tr>
<tr>
<td>status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Error</td>
<td>118</td>
<td>8935.691</td>
<td></td>
</tr>
</tbody>
</table>

ANOVA, analysis of variance.

* P<0.06.

** P<0.001.

outcome (and therefore drug-free status), specifically age, education level, employment status, number of prior treatment episodes, and length of addiction. Student’s t-test and chi-squared analyses did not reveal significant differences on these relevant demographic and psychosocial study variables between drug-free subjects and those still using drugs.

To evaluate the potential combined effects of drug abuse and demographic variables on cold-pressor pain tolerance, subjects were dichotomized, according to classification schemes suggested by Chen and colleagues45 and Peckerman and colleagues,64 as being either pain sensitive (tolerance less than or equal to 180 sec) or pain tolerant (tolerance greater than 180 sec). Nominal measures of using status (using = 1 vs abstinent = 0), primary drug of abuse (opioid = 1 vs cocaine = 0), race (white = 1 vs nonwhite = 0), and employment status (employed = 1 vs unemployed = 0) were entered into logistic regression analysis along with the continuous variables of educational level, years of regular drug use, and number of drug-treatment episodes. This procedure allowed demonstration of how well these variables could, in combination, provide odds on whether a given subject was pain sensitive or pain tolerant. Forward stepwise variable entry was utilized with significance level for model entry and removal set at P=0.05 and P=0.10, respectively.

Table 3 provides the estimated coefficients and related statistics from the logistic regression model. Only using status was a strong enough predictor to be included in the model. The model correctly classified 77% of the cases with a goodness of fit chi-squared statistic not significantly different (P = 0.43, $\chi^2$ [120] = 121.99) from the likelihood value of a calculated perfect model. The analysis indicates that the odds of a subject being pain tolerant (able to tolerate the cold-pressor trial for more than 180 sec) decrease if he is currently using drugs.

**Discussion**

This study sought to assess pain tolerance among drug abusers to provide information that may be useful in improving the management of their pain. In comparison to non-drug-abusing persons, many more drug abusers were pain intolerant (that is, tolerated the CPT for less than 180 sec) than anticipated from the literature, although average cold-pressor pain tolerance for this sample of drug abusers was within normal range. The frequency distribution, not the mean, of pain tolerance differentiates this sample from normative samples.44-47 As a group, these drug abusers are characterized by cold-pressor pain intolerance, which is correlated with current drug use.

Drug-using status was significantly related to pain tolerance, such that abstinent drug abusers were able to tolerate cold-pressor pain almost twice as long as those still using the same drugs. Subjects currently using opioid drugs were the least tolerant of cold pressor pain, followed by current cocaine abusers, abstinent opioid abusers, and finally abstinent cocaine users. This finding provides evidence that the use of these two psychoactive drugs decreases pain tolerance. Pain tolerance as a predominately individual, stable trait is therefore not supported, as the ability to tolerate pain may be more related to whether or not one is abusing certain psychoactive drugs. Decreased pain tolerance is presumably associated with neurophysiological changes in the midbrain reward center that occur in response to chronic drug

**Table 3**
Logistic Regression Model for Predicting Pain Tolerance

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>df</th>
<th>Exp (B)</th>
</tr>
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<tbody>
<tr>
<td>Using</td>
<td>-1.78</td>
<td>0.51</td>
<td>1</td>
<td>0.17</td>
</tr>
<tr>
<td>status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>-0.049</td>
<td>0.27</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Tolerance < 180 sec = 0 (N=28), tolerance > 180 sec = 1 (N = 94).

B, β weight; SE, standard error; df, degrees of freedom; and Exp (B), odds of event occurring.
ingestion. Descending inhibitory pain pathways may be less effective in the presence of drugs that provide euphoria by activating their shared neuroanatomical basis.

Decreased pain tolerance with chronic drug abuse, as opposed to the analgesic effects of acute drug ingestion, is consistent with the concept of a negative reinforcer as described in the Opponent Process Theory. Koob and colleagues predict that psychoactive drugs stimulate the reward system, providing both positive and negative affective processes that, on the whole, typically reinforce continued drug use. The positive reinforcers include feelings of reward and pleasure, and are evident in approach behaviors in laboratory animals. These positive forces are in delicate balance with opposing negative reinforcers, which include feelings of dysphoria, malaise, anhedonia, and avoidance behaviors. Although both originate from the reward system, positive and negative reinforcing processes differ in their temporal and tolerance-producing characteristics. Positive processes outweigh negative ones early in drug use, but tolerance develops rapidly. Negative reinforcing processes build up slowly, becoming more prominent as drug use continues, and are extremely resistant to the development of tolerance. For the chronic drug abuser, then, negative reinforcing processes become predominant. The user does not develop tolerance to these negative affective states, and attempts to achieve relief with continued drug use. The precise neuroanatomy and neurophysiology underlying the opponent processes are not yet understood. As Koob and colleagues state, "While it would appear intuitively logical that the neural elements responsible for 'euphoria' would also be the same elements responsible for 'dysphoria,' associated with drug removal, the cellular events that would mediate such plasticity remain to be discovered."

Analgesia mediated by the brain reward system may be conceptualized as an opponent process in the drug abuser who ingests psychoactive drugs in the absence of pain. Early in drug use, like feelings of reward, the user experiences opioid- and non-opioid-mediated analgesic effects from the psychoactive substance as the brain reward system is activated. Conceptualizing the analgesic effects of abusable drugs as a positive reinforcing process for the drug abuser, tolerance quickly develops to the pain-relieving activity of psychoactive drugs. Over time, the opposing negative process to analgesia, manifested as heightened pain intolerance, becomes the main perceptual state for the drug user.

This theoretical interpretation assumes that dopaminergic systems play a role in pain relief. Such interpretation is not inconsistent with the close interrelationship noted between brain opioid and dopaminergic systems, suggesting that dopaminergic function (which is altered via drugs that produce reward) modulates the functioning of opioid pain systems. Medications with demonstrated dopaminergic activity (that is, tricyclic antidepressants or psychostimulants) are powerful adjuncts to opioid and nonopioid analgesics. Further, Lin and colleagues present compelling evidence that cocaine elicits a supraspinal dopaminergic-mediated nonopioid analgesia in laboratory animals. Although indirect, evidence exists to suspect that changes in pain tolerance in drug abusers may in part be dopamine mediated.

In this study, opioid abusers, whether still using or abstinent, were less cold-pressor pain tolerant than their cocaine abusing counterparts. Although significantly correlated, a significant main effect for drug type on pain tolerance was not established, however. Further evaluation of the relationship between drug type and pain tolerance, regardless of using status, is necessary to determine if changes specific to the endogenous opioid system occur when exogenous opioids are chronically used. As noted, Wise and Bozarth suggest that such changes may be distinct from those occurring in the dopamine-mediated reward center, and may reflect neuroadaptation specific to the endogenous opioid analgesic system. Interestingly, cold-pressor pain tolerance decreased as methadone dose increased for those subjects on methadone maintenance. It should be noted that a normally functioning brain reward system is necessary for opioid drugs to provide their total analgesic effects. The combination of opioid-specific tolerance and negative reinforcing processes within the brain reward system provide rationale for the absence of methadone analgesia for these subjects.

The cross-sectional nature of the data in this study precludes the conclusion that subjects
who are relatively pain tolerant are more likely to be drug free, which would suggest an association between the drug abuser's tolerance for discomfort and his or her ability to become and remain abstinent. In this regard, inherent and stable individual differences in pain tolerance are well documented, and the physical and psychological symptoms of withdrawal are described as uncomfortable and even painful. Those drug abusers who are by nature pain intolerant may have more difficulty becoming abstinent and avoiding relapse than those who are inherently tolerant of discomfort. Subjects still using drugs did not significantly differ from abstinent subjects on any selected demographic or psychosocial variables, implying that pain tolerance may play a role in using status. Pain tolerance did not change with length of abstinence and may be an underlying stable trait. It is possible, therefore, that individuals in the present sample who can tolerate the discomfort associated with withdrawal and craving states, regardless of the drug with which they are associated, may be more likely to become abstinent. Thus, pain tolerance might be a good predictor of treatment outcome in regard to eventual abstinence.

Interpretation of these data is limited by several other factors. Many treatment-seeking drug abusers report a history of polydrug abuse; rarely do they use one drug exclusively. It is possible that cold-pressor performance was influenced by the neurophysiological effects of several psychoactive substances in addition to the identified primary drug, despite the lack of intoxication at the time of testing. This is likely to be the case for the 18 methadone-maintained subjects who reported concurrent cocaine use; the pain tolerance of those subjects was less than that of pure cocaine abusers but greater than that of methadone-maintained subjects who denied recent cocaine use. Also, subjects may not have been tested in equivalent psychopharmacological states. Although screened for intoxication, opioid abusers are always either "under the influence" or in a state of withdrawal. Conversely, cocaine abusers typically spend substantial periods of time drug free. Persons classified as drug free might be suffering from nonequivalent temporal effects of abstinence. Withdrawal, craving, and protracted abstinence syndromes all occur in physiologically drug-free states and are qualitatively different. It is unclear how uncontrolled drug-related psychological states might have affected the results.

Despite these limitations, the results suggest that persons actively abusing psychoactive drugs have decreased tolerance for acute monophasic pain, and therefore their complaints of discomfort related to injury, illness, or surgical intervention should be taken seriously and managed aggressively. This pain intolerance appears augmented in active opioid addicts, perhaps related to the combined effects of opioid-specific tolerance and negative reinforcing processes within the brain reward system. Related to these, stable methadone maintenance appeared to provide no analgesic effect; rather, higher doses were actually associated with lower pain tolerance.

Basic animal research is necessary to demonstrate the neuroadaptive changes in response to chronic drug abuse, which are evident as decreased pain tolerance. The complex neurophysiology of drug dependence is less than completely understood, and specific changes that would impact on pain tolerance cannot be more than tentatively described. Future research on pain tolerance in drug-dependent experimental animals will enable further elucidation of the neurophysiology underlying addiction and pain tolerance, and, more generally, the function and plasticity of the reward center.

Future research is also needed to replicate the current findings and explore within an experimental design the relationship between pain tolerance and psychoactive drug use of all types. Further, the effectiveness of opioid analgesics in relieving pain in a wide variety of drug abusers must be examined. Significant clinical questions include: If methadone maintenance relates to pain intolerance, are opioids an appropriate analgesic for methadone-maintained patients? If negative reinforcing processes dominate in the brain reward systems of drug abusers, nonpharmacological strategies to activate opioid- and non-opioid-mediated analgesia may not be effective in these persons, and should be evaluated.

Finally, pain tolerance over the natural history of addiction must be examined. Do persons become less pain tolerant as their addiction develops? Does pain tolerance in-
crease with abstinence? How long do potential neuroadaptive changes related to drug use persist? Do underlying inborn differences in pain tolerance predict which drug abusers will be successful in managing the discomfort associated with withdrawal and abstinence? Longitudinal designs are necessary to determine the causal relationship between drug abuse and pain tolerance.

Clearly, drug abuse and pain tolerance are psychobiologically interrelated. By studying patterns of coexistence between the two phenomena, each may be better understood. Drug abusers in pain, as well as persons experiencing chronic pain who are dependent on drugs, present complex clinical management challenges, and until the relationships between the two are elucidated, the care these persons receive will continue to be less than ideal. Although preliminary, these findings provide evidence that pain tolerance is lessened when persons actively abuse psychoactive drugs. Clinically, complaints of pain from this population should be considered genuine, drug dependence must be considered integral to pain tolerance, and nontraditional or innovative pain relieving interventions may be required.

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