

A PROSPECTIVE EVALUATION

PROSPECTIVE EVALUATION OF PATIENTS WITH INCREASING OPIATE NEEDS: PRESCRIPTION OPIATE ABUSE AND ILLICIT DRUG USE

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Background: Multiple aberrant behaviors have been described to identify patients abusing opioids and using illicit drugs. However, patient behavior encompassing aggressive seeking or complaining about the need for higher doses of opioids has not yet been evaluated with regards to misuse or abuse patterns of prescription drugs and illicit drug usage.

Objective: The objective of this study was to evaluate and identify the prevalence of illicit drug use and prescription drug abuse or misuse in patients seeking higher doses of opioids and compare to a group of patients not seeking higher doses of opioids.

Design: A prospective, non-random-

ized, consecutive, observational study.

Methods: A total of 200 patients from an interventional pain management setting with 100 consecutive patients in each group either not seeking additional opioids (Group I) or seeking higher doses of opioids (Group II) were evaluated with urine testing for illicit drug use, and/or misuse or abuse of opioids.

Drug testing was carried out by Rapid Drug Screen®.

Results: Results of this study showed a significantly greater proportion of patients in Group II using illicit drugs (15% vs 32% $P = 0.005$). Combined use of illicit drugs and abuse of non-prescribed opioids

was also present in a significantly greater proportion of patients in Group II (15% vs 39% $P = 0.000$). A significant number of patients in Group I (32%) and Group II (30%) failed to show the prescribed drug in their urine.

Conclusion: A significant proportion of patients, whether they were seeking additional opioids or not, used illicit drugs. Further, a greater proportion of patients in Group II used illicit drugs and non-prescribed opioids.

Keywords: Illicit drug use, controlled substance abuse, misuse, drug dependence, aberrant behavior

Findings from the 2002 National Survey on Drug Use and Health estimated that about 14.6 million persons used marijuana, 2.0 million used cocaine, and 1.2 million used hallucinogens (1). An estimated 6.2 million persons, or 2.6% of the population age 12 or older, were current users of psychotherapeutic drugs taken non-medically with 4.4 million using pain relievers, 1.8 million using tranquilizers, 1.2 million using stimulants, and 0.4 million using sedatives. In addition, an estimated 11.0 million persons reported driving under the influence of an illicit drug during 2002, which corresponded to 4.7% of the population age 12 or older. This survey (1) also showed that approximately 1.9 million persons age 12 or older had used OxyContin®

non-medically at least once in their lifetime, which increased from 957,000 such users in 2001, reaching the same level as cocaine use for the first time.

Prescription-controlled substances are commonly utilized in chronic pain as monotherapy or in conjunction with other modalities, including physical therapy and interventional techniques. Opioids are administered in minor to moderate dosages in patients responding to interventional techniques as an adjunct therapy, with satisfactory results of pain management and functional improvement (3). Consequently, an increasing number of studies have been published focusing on the need of opioids in chronic pain, assessment for addiction, and adherence monitoring (2-10). Multiple guidelines also have been developed in providing opioids to chronic pain patients (3, 4). Similarly, an increasing number of studies have documented the relatively high incidence of controlled substance abuse and illicit drug use in patients undergoing treatment for chronic pain (11-15). Katz et al (7) in evaluating the results of behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy, reported that 43% had a problem present-

ing with either a positive urine drug toxicology or one or more aberrant drug-taking behaviors. Manchikanti et al (12-15) showed that the overall prevalence of controlled substance abuse in an interventional pain management practice setting was 18% to 24% (13, 14); whereas they identified illicit drug use in 14% to 16% of patients without controlled substance abuse, and 34% of patients with controlled substance abuse (12, 15).

Multiple authors (3-10, 16-18) have attempted behavioral assessments and screening tools to identify the abuse of controlled substances. Kirsh et al (16) described a set of behaviors less indicative of aberrancy, which included aggressive complaining about the need for higher doses, along with drug hoarding during periods of reduced symptoms, acquisition of similar drugs from other medical sources, unapproved use of drugs to treat another symptom, unsanctioned dose escalation one or two times, reporting psychic effects not intended by the clinicians, and requesting specific drugs. Others have described pseudoaddiction and opioid phobia as responsible for misinterpretation of drug seeking behavior (19-24). Many pain specialists and primary care

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physicians enthusiastically embraced the possibility of long-term opioid therapy for the treatment of chronic pain without realizing the consequences of dependency, abuse, and diversion. They have only focused on appropriate pain management, pseudoaddiction, and opiophobia. Kirsh et al (16) described pseudoaddiction as the term used to delineate the distress in drug-seeking behaviors similar to those of addicts, that can occur in the context of unrelieved pain. Robinson et al (19) described pseudoaddiction as a clinical term that describes patients who seem to be drug seeking and who try to increase their medication usage, a behavior believed to be motivated by an inadequate level of pain relief. Many other influential authors (18, 20-22) embraced the phenomenon and advocated it. However, these assertions, expert opinions, and conclusions are derived from one case report describing a single patient by Weisman and Had-dox (23). Similarly, opiophobia was described as fear of the addiction potential of opioid analgesics, which may result in undertreatment of chronic pain, with detrimental effects on pain management, by Morgan in 1986 (24). Thus, there is no consensus on what constitutes the behaviors indicative of aberrancy and the characteristics common to these patients.

We believe that all the characteristics described by Kirsh et al (16) indicate drug abuse phenomena, including aggressive complaining about the need for higher doses. It has been shown repeatedly that abuse or misuse of controlled substances, along with illicit drug use, is prevalent, coupled with inaccuracies in the patient's self-report of drug use. It has been shown that patients with chronic pain tend to underestimate their medication usage (25) and regularly provide incorrect information on illicit drug use (26).

In this prospective evaluation, we sought to evaluate illicit drug use and controlled substance abuse in patients aggressively requesting higher doses of opioids or complaining about the need for higher doses.

METHODS

A total of 200 consecutive patients, with 100 in each group; Group I patients without a request for additional medication, and Group II patients with requests or aggressive complaints about increasing dosages.

All patients were in the treatment program in an interventional pain management setting receiving interventional techniques along with opioids. Their condition was considered as stable and pain was reasonably controlled by the physician, based on current dosage, response to interventional techniques, and functional status. If dosage was judged to be unstable and pain control was poor, they were excluded from the study. All the patients were receiving stable doses of either hydrocodone, oxycodone (7.5 mg to 10 mg q 8 hrs or 6 hrs), methadone (30 mg to 60 mg daily), or long acting morphine (60 mg to 120 mg daily) by the treating physician.

All patients signed an informed consent for random drug monitoring and the publication of results, without identification of individuals. Appropriate precautions were taken to protect the privacy and identity of patients participating in this evaluation.

Drug abuse or misuse was considered if a patient tested positive for a non-prescribed opioid. Potential misuse was considered if the prescribed drug was not detected in urine testing. Positive drug screen for cocaine was considered definite by Rapid Drug Screen*. Positive metham-

phetamine, amphetamines, or marijuana (THC) were also checked for false-positives with a follow-up laboratory evaluation, and a history of drugs causing false-positive results. The positive results confirmed by laboratory evaluation were considered as positive.

Rapid Drug Screen was performed on all patients participating in the study. It is a one-step, lateral flow immunoassay for the simultaneous detection of up to 9 drugs by urine analysis. Each analysis occupies a separate channel, intended for use in the qualitative detection of various drugs.

Data were recorded on a database using Microsoft® Access® 97. The SPSS version 9.0 Software was used to generate the frequency tables and the chi-squared statistic was used to test the significant difference between groups. Fisher's exact test was used wherever expected values were less than 5. Student's t-test was used to test mean significant differences between groups. The prevalence and 95% confidence intervals (CI) were calculated. Results were considered statistically significant if the *P* value was less than 0.05.

RESULTS

A total of 200 patients were evaluated with a rapid drug screen. Their urine was tested for the following drugs: cocaine, opioids, methadone, amphetamines, cannabinoids, barbiturates, benzodiazepines, methamphetamine, and phencyclidine.

Patient Flow

The 200 patients included in the study were selected from a total sample of 426 patients seen in an interventional pain management practice by one physician over a period of 2 months. One hundred and six patients were selected for Group I who were not seeking additional

Table 1. *Prevalence of illicit drug use**

	Group I (100)		Group II (100)		P Value
	Number of Patients	95% CI	Number of Patients	95% CI	
Cocaine	1	0%-5%	8	3%-15%	0.035
Marijuana (THC)	14	8%-22%	21	13%-30%	0.193
Amphetamine/ Methamphetamine	1	0%-5%	1	0%-5%	0.621
Combined use of cocaine and marijuana	1	0%-5%	4	1%-10%	0.369
Totals	15	9%-24%	32	23%-42%	0.005

* Totals may not correlate as some patients were in more than one category
CI - confidence intervals

Table 2. *Combined use of illicit drugs and misuse of prescription drugs**

	Group I		Group II		P value
	Number of Patients	95% CI	Number of Patients	95% CI	
Illicit drug use	15	9%-24%	32	23%-42%	0.005
Non-prescription opioid use	0	0%	7	3%-14%	0.014
Combined use and misuse	1	0%-5%	4	1%-10%	0.369
Total use and misuse	15	9%-24%	39	29%-49%	0.000

*Totals may not correlate as some patients were in multiple categories

CI - confidence intervals

medication from the initial sample of 148 patients. Of the 106 patients, 6 failed to provide the urine sample. From the initial sample, 34 patients were included in Group II and the remaining patients were obtained from the total of 426 patients. Overall, 114 patients were selected to obtain a sample of 100 as 14 patients, either failed (8) or refused (6) to provide the urine sample.

Demographic Characteristics

Gender distribution was 36% men in Group I compared to 42% in Group II. Age was (mean \pm SD) 49.1 ± 12.4 yrs in Group I and 46.2 ± 12.2 yrs in Group II with a range of 23 to 76 in Group I and 21 to 85 in Group II. There were no significant differences noted between groups I and II, either in gender or age distribution.

Illicit Drug Use

As illustrated in Table 1, 15% (95% CI, 9%-24%) of the patients in Group I used illicit drugs, whereas 32% (95% CI, 23%-42%) of the patients in Group II used illicit drugs ($P = 0.005$).

Combined Use of Illicit Drugs and Misuse of Opioids

Table 2 illustrates combined use of illicit drugs and misuse of opioids. An illicit drug was seen in 15% (95% CI, 9%-24%) of the patients in Group I and 32% (95% CI, 23%-42%) in Group II ($P = 0.005$). Non-prescription opioid usage was seen in 0% in Group I and 7% (95% CI, 3%-

14%) in Group II, and combined use and misuse of drugs was seen in 15% (95% CI, 9%-24%) in Group I and 39% (95% CI, 29%-49%) in Group II ($P = 0.000$).

Misuse or Abuse of Opioids

As illustrated in Table 3, the prescribed opioid was absent in 32% (95% CI, 23%-42%) of the patients in Group I and 30% (95% CI, 21%-40%) of the patients in Group II. A non-prescription opioid in the urine was detected only in Group II in 7% (95% CI, 3%-14%) of the patients.

DISCUSSION

This evaluation of illicit drug use with or without opioid abuse or misuse illustrated significant differences in patients satisfied with their opioid therapy compared to patients seeking additional opioids. This study showed that illicit drugs were used by 15% (95% CI, 9%-24%) of the patients in Group I seeking no additional opioids compared to 32% (95% CI, 23%-42%) in Group II seeking additional opioids. In addition, in Group II, 7% of the patients also were using non-prescribed opioids. Both illicit drugs and non-prescribed opioids were detected in a greater proportion of patients in Group II. Total use of illicit drugs and misuse of non-prescription opioid use was detected in 15% (95% CI, 9%-24%) of the patients in Group I and 39% (95% CI, 29%-49%) in Group II. However, there were no differences in patients with an absence of prescribed drug in their urine with 32%

in Group I and 30% in Group II. The results of this study confirmed the use of illicit drugs and abuse of prescription opioids in both groups of patients. However, a greater proportion of patients in Group II, those aggressively seeking increased doses of opioids, abused illicit drugs and prescription opioids.

This is the first study to evaluate a behavioral pattern with increasing need for higher doses as an indicator of illicit drug use and abuse of opioids. Patients with aggressive complaining about the need for higher doses of opioids use more illicit drugs, including amphetamines and cocaine, along with non-prescribed opioids. Cocaine was used by 1% in Group I and 8% in Group II. The marijuana usage was 14% in Group I and 21% in Group II. Combined use of cocaine and marijuana, as well as combined use of illicit drugs and opioids was seen in a greater proportion of patients in Group II.

Kirsh et al (16) described that patients with pseudoaddiction with unrelieved pain may become so dramatic that some patients appear to return to illicit drug use as a means of self-medication, whereas others show blatant patterns of behavior that may also raise concerns regarding the possibility of true addiction (20, 21). Some believe that the intent of these behaviors may be difficult to discern in the context of unrelieved symptoms.

Based on the results of this study, we propose that pseudoaddiction is terminology which should be abandoned and patients must be evaluated appropriate-

Table 3. *Misuse or abuse of opioids*

	Group I		Group II		P value
	Number of Patients	95% CI	Number of Patients	95% CI	
Absence of prescribed drug in urine	32	23% - 42%	30	21% - 40%	0.760
Presence of non-prescription opioid in urine	0	NA	7	3% - 14%	0.014

CI - confidence intervals

ly not only for undertreatment of pain, but also for appropriate use of opioids and inappropriate use of illicit drugs and opioids. Katz et al (7) proposed that it is important to recognize illicit or non-prescribed drug use in chronic pain patients who are being treated with opioids as they may suffer from the disease of addiction, and physicians may not have other means of making this important diagnosis. Further, the treatment for addiction is possible because patients may be harmed with combined use of multiple drugs by not identifying the issue and by not providing appropriate treatment. Thus, physicians may not be helping patients who use opioids in combination with illicit drugs, as well as other opioids.

Abuse may be corrected either by drug detoxification from opioids in an appropriate setting or simply by counseling and stopping the prescription of opioids. If patients are randomly monitored, it also provides validation for patients who use their drugs as prescribed and also do not abuse illicit drugs. Identification of inappropriate drug use also will reduce the illegal market for the drugs prescribed by physicians and the street purchase of prescription drugs, as well as illicit drugs. However, application of the results of urine drug testing and behavioral monitoring in the context of comprehensive evaluation and management of chronic pain is essential. Patients should be identified so that these drugs are not used for other purposes, either legitimate purposes such as unidentified disorders or pain problems or illegitimate usage such as abuse and diversion.

As identified in many studies, among all the illicit drugs, marijuana is the most widely abused and readily available illicit drug in the United States. Its use has been estimated in 14.6 million or 6.2% of the population age 12 or older (1). Further, marijuana is also used repeatedly. It was shown that among marijuana users in 2002, approximately one-third or 4.8 million persons, used it on 20 or more days in the past month. The use of marijuana or hashish produces feelings of relaxation and well-being and impairs cognitive function and performance of psychomotor tasks (27). A high incidence of cannabis consumption has been reported among patients with schizophrenia (28). Symptoms of withdrawal – restlessness, irritability, and insomnia – are subtle and appear in heavy users (29). Panic attacks

and psychosis have been reported with overdose (30). The long-term effects of high doses of cannabinoids is a complex and controversial subject. Even though, long-term use of cannabis impairment of memory is evident (31, 32), the cause of marijuana amotivational syndrome – loss of energy and drive to work – remains unclear (30). Cannabinoid abuse and addiction have been attributed to G-protein-coupled cannabinoid CB₁ receptors, which are richly distributed in basal ganglia and cerebral-cortex regions (27). Similar to previous studies (6, 8, 9, 12-15), this study shows marijuana to be the most commonly abused drug with a prevalence of 14% in Group I and 21% in Group II. It is higher in both groups compared to the general population, with marijuana usage of 6.2% (1).

Cocaine is the second most commonly abused drug. An estimated 2 million persons or 0.9% of the population were current cocaine users in 2002 (1). However, cocaine use has been increasing gradually from 0.5% in 2000 to 0.9% of the population in 2002. Cocaine is a potent blocker of the dopamine-, norepinephrine-, and serotonin-uptake transporters (27). Cocaine is a powerful addictive drug (33). Smoking crack can cause severe chest pains with lung trauma and bleeding (34). Cocaine-related deaths are often a result of cardiac arrest or seizures followed by respiratory arrest (34). Compared to the general population, cocaine use was similar in Group I, whereas it was significantly higher in Group II, with 8% of patients using cocaine.

Methamphetamine and amphetamine are also known as meth, poor man's cocaine, crystal meth, ice, glass, etc. Short-term administration of methamphetamine and amphetamine produces euphoria, a feeling of well-being, and alertness, as well as increased arousal, concentration, and motor activity (27). These substances increase blood pressure and the pulse rate and induce the release of corticotropin-releasing factor, corticotropin, and cortisol (35-37). Long-term use may cause irritability, aggressive, and stereotyped behavior, and paranoid-like psychosis (27). While craving is extremely intense, signs of withdrawal can be mild, characterized by depression, lack of energy, and insomnia (38). Acute intoxication with amphetamine or methamphetamine may result in serious consequences manifested by cerebral hemorrhage, the

serotonin syndrome, psychosis, panic, hyperthermia, and heat stroke (27). Characteristic features of serotonin syndrome have been described as altered mental status, autonomic instability, and neuromuscular abnormalities resulting in hyperthermia. Multiple derivatives of amphetamine may have toxic effects on dopamine and serotonin neurons (39, 40). Amphetamines and methamphetamines in this study were found in 1%.

The study may be criticized for utilizing rapid drug screening instead of Gas Chromatography/Mass Spectroscopy (GC/MS), or enzyme immunoassay. However, rapid drug screening utilizes enzyme immunoassay and has been shown to be valid. It is a good screening tool providing testing of multiple drugs, rapidly and inexpensively. A side-by-side comparison of rapid drug testing with GC/MS yielded over 90% correlation for various drugs. Percent agreement with GC/MS was 91% for THC, 93% for cocaine, over 96% for methadone, over 95% for opioids, 96% for amphetamines and methamphetamines, and 99% for barbiturates. Thus, we believe that the results are reasonably accurate. However, one should exercise caution if the patient is denied future treatment based on these results. Results should be accurately confirmed with laboratory testing utilizing GC/MS.

The results of this evaluation showed that illicit drug use and misuse of prescription-opioids are common in chronic pain patients seeking higher doses of opioids compared to patients who are not seeking higher doses. However, a significant proportion of patients who are not seeking higher doses of opioids also abuse marijuana at a rate higher than the general population. Urine toxicology provides significant insight into illicit drug use and controlled substance abuse.

CONCLUSION

A significant proportion of patients receiving controlled substances were shown to use illicit drugs, as well as non-prescribed opioids. However, the proportion was greater in patients who were seeking additional opioids compared to patients who were not seeking additional opioids. Further, a significant proportion of patients in both groups were non-compliant with drug use as the prescribed drug was absent in their urine specimens.

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