Psychological factors as predictors of opioid abuse and illicit drug use in chronic pain patients

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ABSTRACT

Background: *Psychopathology (depression, anxiety, somatization disorder) and substance abuse (opioid misuse and illicit drug use) are common in patients with chronic pain and present problems for public health and clinical management. Despite a body of literature describing various methods for identifying psychopathology, opioid misuse, and illicit drug use in chronic pain patients, the relationship between psychopathologies, substance abuse, and chronic pain has not been well characterized.*

Methods: *This report describes a total of 500 consecutive pain patients prescribed and receiving stable doses of opioids. The patients were evaluated for psychopathology, opioid abuse, and illicit drug use during the course of regular pain management treatment. The relationships between psychopathology and drug abuse and/or illicit drug use in chronic pain patients were examined, and psychological evaluation for depression, anxiety, and somatization disorder was performed.*

Results: *Depression, anxiety, and somatization disorder were documented in 59, 64, and 30 percent of chronic pain patients, respectively. Drug abuse was significantly higher in patients with depression as compared to patients without depression (12 percent with depression versus 5 percent without). Current illicit drug use was higher in women with depression (22 percent) than women without depression (14 percent) and in men with or without depression (12 percent). Current illicit drug use was also higher in men with somatization disorder (22 percent) than men without (9 percent).*

Conclusion: *This study demonstrated that the presence of psychological features of depression and somatization disorder may be markers of substance abuse diathesis in chronic pain patients.*

Key words: psychopathology, substance abuse, opioid abuse, illicit drug use, MCMI, P3, DSM-IV-TR, endophenotype

INTRODUCTION

Pain is defined as both a physiological sensation and a psychological condition or state.[1] Thus, the neural event of pain is in many ways inextricable from the psychological or phenomenal experience of pain.[2] Chronic pain in particular manifests a psychological constellation of cognitive, emotional, and behavioral characteristics.[3] There is extensive literature associating chronic pain and psychological disorders.[2-28] Numerous studies have shown that a significant proportion of pain patients present with depression, anxiety, and somatization disorder, either alone or in combination.[4-28] In studies that have evaluated chronic pain patients, the comorbidity of major depression ranged from 15 percent to 56 percent, significantly higher than the occurrence of major depression within the general (i.e., non–chronic pain) population, which ranged from 5 percent to 10 percent. Similarly, the occurrence of somatization disorder ranged from 20 percent to 31 percent in chronic pain patients, compared to 1 percent to 4 percent in the general population. Thus, it becomes evident that 1) psychological factors are reciprocally interactive in the initiation and expression of the pathology of chronic pain; 2) unrecognized and untreated psychopathology may increase pain intensity, disability, and exacerbation of environmental influences; 3) this reflects the truly biopsychosocial dimensionality of chronic pain, and, therefore, 4) such dimensions must be considered in any meaningful paradigm for chronic pain management.[5-8]

A considerable amount of research has been devoted to profiling the psychological and behavioral characteristics of chronic pain patients in an attempt to accurately

identify strategies and tactics of effective co-management of psychological and physical symptoms and the combined effects of disability (e.g., anxiety has been shown to decrease patients' pain threshold and tolerance, and both anxiety and depression have been associated with magnification of medical symptoms).[10,11,23] Yet a persistent problem is the overuse/abuse of both prescription drugs and illicit agents in this patient population. Surveys have shown that persons with a history of at least one major depressive episode within the past year were significantly more likely to have used illicit drugs during that time period compared to those persons without a major depressive episode (28.8 percent versus 13.8 percent), and substance dependence or abuse was more prevalent among persons with a major depressive episode than among nondepressed persons (22.0 percent versus 8.6 percent). Similarly, serious psychological distress was highly correlated with substance dependence or abuse: 21.3 percent (4.6 million) of adults with serious psychological distress were shown to be dependent on or to have abused alcohol or illicit drugs in 2004, as compared to only 7.9 percent of adults without serious psychological distress. Similarly, the risk and prevalence of substance abuse has been associated with pre- and comorbidity of psychological disorders in patient populations receiving controlled substances.[29-35] Regier et al.[34] demonstrated that patients with a lifetime mental disorder present with more than twice the risk of having an alcohol disorder and over four times the risk of having (another) substance abuse disorder. Webster and Webster[29] have shown that depression is a risk factor for opioid abuse (as ascertained by the Opioid Risk Tool), although Ives et al.[36] failed to reveal a direct correlation between depression and opioid misuse.

The potential magnitude of this problem becomes evident when one considers that, according to the 2004 National Survey on Drug Use and Health, there were 35.1 million (14.7 percent) persons aged 12 or older who had had at least one major depressive episode in their lifetime. Of these, 19.3 million persons (8.1 percent of the population) had had a major depressive episode in the past 12 months, including 2.2 million youths (aged 12 to 17) and 17.1 million adults (aged 18 or older). This survey also estimated the prevalence of serious psychological distress, defined as a high level of distress due to any type of mental problem. In 2004, there were 21.4 million adults with serious psychological distress, representing 9.9 percent of all adults.[37]

Despite the noted increase in the prevalence of pain, psychological, and substance abuse disorders and the growing body of evidence to support the comorbidity (and putative relationship) of these disorders, there is sparse literature addressing the viability of psychological factors as predictors of opioid abuse and/or illicit drug use in chronic pain patients. Controlled substance abuse among chronic pain patients is common. The prevalence of prescription drug overuse and abuse has been reported to be between 9 and 41 percent for patients receiving opioids for chronic pain. This is particularly significant, given that as many as 90 percent of patients in pain management settings receive opioids for chronic pain.[38-47]

Recently, we have evaluated multiple variables that may be useful in identifying controlled substance abuse and illicit drug use in chronic pain patients.[38] Our work has revealed that pain resulting from motor vehicle accidents, involvement of multiple painful sites, and a past history of illicit drug use were all significant risk factors. In addition to these variables, Ives et al.[36] identified past cocaine abuse, drug or DUI conviction, and past alcohol abuse as predictors of misuse.

In light of the fact that drug use represents a significant epidemiological problem, compounds the impact of chronic pain and psychological conditions, and considerably complicates (if not impedes) effective care, tactics for the detection and reduction/prevention of continued drug misuse/abuse assume an important place in the initiation of therapeutic intervention. Multiple investigators have described screening instruments to detect opioid abuse or misuse in chronic pain patients.[38,45,48-57] However, most of the screening instruments currently in use have not included or accounted for psychological variables.

Our earlier work evaluated depression as a variable.[38] However, our study was limited in that it did not consider the broader effects of pain and comorbid psychopathologies as part of a spectrum disorder (or disorder continuum), and therefore did not examine patterns or the role of anxiety and somatization disorder as covariables in drug misuse/abuse in chronic pain patients. The hypothesis that chronic pain and these disorders may be covariant is strengthened by the findings of Dersh et al.,[11] according to which chronic pain patients were 10.2 times more likely than persons in the general population to have a major Axis I psychiatric disorder. The Dersh et al.[11] evaluation of Axis I disorders included drug abuse and alcohol abuse/dependence, as well as major depression, dysthymia, any anxiety disorder, and panic disorder. Their study showed that drug abuse and dependence were present in 10.7 percent of the patients. There was a correlation between the occurrence of pain and several types of pathologies classified in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), most notably major depressive disorder, drug abuse/dependence, and personality disorders, although anxiety disorders were less frequent than major depressive disorders.

Therefore, given that pain is by definition both a physiological and psychological event, and considering the reported relationship between particular Axis I psychological disorders (e.g., depression, anxiety, somatization)

and substance abuse, we pose the question of whether determination of psychological presentation (i.e., the presence of co- and/or premorbid psychological disorder[s]) may have some value toward predicting (or alerting to) the predisposition/sensitivity to substance abuse in chronic pain patients. Thus, this study investigated the pattern of depression, anxiety, and somatization disorder in chronic pain patients who were either misusing opioids or using illicit drugs in an attempt to correlate these findings and better clarify the value of psychological condition as a predictor of substance abuse among chronic pain patients in interventional pain management settings.

METHODS

This article reports the results of routine psychological testing for 500 consecutive patients taking prescribed opioids for pain management through a private practice in an interventional pain management setting. All patients provided valid and informed consent for obtaining information on drug use, random drug testing, and confidential publication of results. Appropriate precautions were taken to protect the privacy and confidentiality of patients participating in this evaluation. All patients also signed agreements that included permission to contact pharmacies and physicians and to perform random drug screening. All patients in this study were receiving stable doses of hydrocodone, oxycodone, methadone, or morphine in pharmacologic support of interventional pain management techniques. In this way, opioid use constituted supplemental pain management and was not the mainstay of the treatment protocol. Inclusion criteria for data evaluation required that patients were willing to participate, were in stable condition, and were in a pain management program encompassing interventional techniques and opioid drug administration. Exclusion criteria were defined as an inability to understand the consent, refusal to sign the consent, refusal to follow the terms of the agreement, refusal to submit to random drug testing, and unstable pain control.

Upon inclusion, initial evaluation consisted of monitoring controlled substance intake—with special focus upon externally provided drugs—and documentation of past history of illicit drug use. History of illicit drug use was determined from patients' reports of such use/activity.

Data collected included information from records, pharmacies, referring physicians, and all physicians involved in patient treatment. Data were collected using a preprinted format including demographic information and drug history and were compared with all acquired information.

Rapid urine drug screening (Instant Technologies, iCup®, Norfolk, VA) was performed on all the patients participating in the study. The rapid drug screen is a one-step, lateral-flow immunoassay for the simultaneous detection of up to nine drugs via urinalysis. Each analysis occupies a separate channel intended for use in the qualitative detection of various drugs.

Psychological evaluation focused on signs and symptoms that were representative of the DSM-IV-TR characterizations of depression, anxiety, and somatization disorder. Psychological status was evaluated by obtaining a psychological history using a DSM-IV-TR criteria-based questionnaire, followed by a physician-conducted interview and/or administration of the Millon Clinical Multiaxial Inventory (MCMI-II or MCMI-III) and/or administration of the Pain Patient Profile (P-3®).[58-60] Evaluation using the DSM-IV-TR criteria-based questionnaire involved multiple questions with content validity for determinations of clinically relevant features of depression, anxiety, and somatization disorder.[4,58]

The MCMI is a 175-question psychological tool that does not require administration by a psychologist, is commonly utilized to evaluate psychological involvement in various medical syndromes, and is easily administered in outpatient interventional pain practices.[59] The MCMI evaluates personality disorders and various clinical syndromes including depression, generalized anxiety, and somatoform disorder.

The P-3 is a 34-item instrument for briefly assessing psychological characteristics known to affect the pain perception and treatment response of pain patients.[60] It is somewhat specifically used to evaluate comorbidity of depression, anxiety, and somatization in pain patients.

A prospective evaluation of the effectiveness of the DSM-IV-TR questionnaire, pain management questionnaire, and clinical interview showed these techniques to reliably assess depression and anxiety in an interventional pain management setting.[4] Therefore, diagnostic impressions of psychological conditions were based on the results of these tests throughout the (opioid) treatment period.

Substance abuse was operationally defined as occurring 1) when patients received controlled substances from any place or source other than the prescribing physician, with the exception of the short-term use of controlled substances for acute injury/insult and/or emergency, and/or 2) when patients escalated the use of controlled substances beyond the dose(s) and schedule prescribed. Drug trafficking was defined according to the legal determination as described by statute and in courts of law. Past history of illicit drug use was based on patient report/history and/or information afforded by the patient's medical record.

All patients underwent rapid urine drug testing. Patients were considered positive for current illicit drug use if one of the monitored illicit drugs (including cocaine, marijuana [THC], amphetamines, or methamphetamine) was detected by urinalysis, with the qualifying conditions that 1) positive results for the presence of

Table 1. Demographic characteristics				
		Male **n = 205 (41 percent)**	**Female** **n = 295 (59 percent)**	**Total** **N = 500**
Age (years)	< 45	65 (32 percent)	123 (42 percent*)	188 (38 percent)
	45 to 64	121 (59 percent)	133 (45 percent)	254 (51 percent)
	≥ 65	19 (9 percent)	39 (13 percent)	58 (11 percent)
	Range	25 to 77	21 to 78	21 to 78
	Mean ± SE	49.5* ± 11.1	48.0 ± 13.2	48.6 ± 12.4
Duration of pain (years)	< 5	44 (22 percent)	78 (26 percent)	122 (24 percent)
	5 to 9	60 (29 percent)	81 (28 percent)	141 (28 percent)
	≥ 10	101 (49 percent)	136 (46 percent)	237 (47 percent)
	Range	1 to 44	1 to 44	1 to 44
	Mean ± SE	11.6* ± 9.2	10.1 ± 7.5	10.7 ± 8.2
Mode of onset	Gradual onset	58 (28 percent)	129 (44 percent*)	187 (37 percent)
	Motor vehicle accident	38 (19 percent)	62 (21 percent)	100 (20 percent)
	Other incident	48 (23 percent)	65 (22 percent)	113 (23 percent)
	Work-related injury	61 (30 percent*)	39 (13 percent)	100 (20 percent)
Number of regions involved	one region	95 (46 percent)	85 (29 percent)	180 (36 percent)
	two regions	82 (40 percent)	158 (54 percent*)	240 (48 percent)
	three regions	28 (14 percent)	52 (18 percent)	80 (16 percent)
History of previous spine surgery		96 (47 percent*)	80 (27 percent)	176 (35 percent)
Insurance status	Third-party	76 (37 percent)	116 (39 percent)	192 (38 percent)
	Medicare with/without third-party support	80 (39 percent*)	74 (25 percent)	154 (31 percent)
	Medicare and Medicaid	28 (14 percent)	57 (19 percent)	85 (17 percent)
	Medicaid	21 (10 percent)	48 (16 percent)	69 (14 percent)
Past history of illicit drug use		33 (16 percent)	47 (16 percent)	80 (16 percent)

* Indicates a significant difference between male and female patients.

Table 2. Psychological characteristics

	Depression		Anxiety		Somatization disorder	
	Positive	**Negative**	**Positive**	**Negative**	**Positive**	**Negative**
Male (n = 205)	111 (54 percent)	94 (46 percent)	119 (58 percent)	86 (42 percent)	55 (27 percent)	150 (73 percent)
Female (n = 295)	185 (63 percent)	110 (37 percent)	200 (69 percent*)	95 (32 percent)	96 (32 percent)	199 (68 percent)
Total (N = 500)	296 (59 percent)	204 (41 percent)	319 (64 percent)	181 (36 percent)	151 (30 percent)	349 (70 percent)

* Indicates a significant difference between male and female patients.

cocaine (and its metabolites) was considered definite by rapid urine drug screen, and 2) positive identification(s) of methamphetamine, amphetamine, and/or marijuana were checked for false positives with a follow-up laboratory evaluation and exclusion of drugs causing false-positive results. For example, tentatively positive THC results were confirmed with secondary laboratory testing if a patient was on pantoprazole (Protonix®) or denied using marijuana. All results confirmed by secondary laboratory evaluation were considered final.

Data were tabulated using Microsoft Access® 2003, and SPSS (version 9.0) was used to generate frequency tables. The χ^2 statistic was used to determine significant differences between groups. Fisher's exact test was used post hoc (wherever the expected value was less than five). Student's t-test was used to determine significant sex-based differences. All results were considered statistically significant at p < 0.05.

RESULTS

Patient flow

Data were evaluated for the prevalence of opioid abuse and illicit drug use in 500 patients. Initially, 566 patients were eligible, but 66 patients refused to participate in the study. All patients were evaluated for opioid abuse and underwent urinalysis for cocaine, amphetamines, methamphetamine, and marijuana (THC).

Demographic characteristics

Table 1 illustrates the demographic characteristics of age, duration of pain, mode of onset of pain, number of body regions involved, history of previous spine surgery, insurance status, and past history of illicit drug use among male and female patients.

The proportion of female patients was higher in the age group of those younger than 45 years (42 percent versus 32 percent), whereas the proportion of male patients was higher in the 45-to-64 age group (59 percent versus 45 percent). Mean age was slightly higher for males (49.5 years versus 48.0 years).

The duration of pain was evaluated in three groupings: less than five years, five to nine years, and 10 years or longer. Overall, 75 percent of the patients had had pain for more than five years, and 47 percent had had pain for more than 10 years. Mean duration of pain was longer in males (11.6 years versus 10.1 years).

Thirty-seven percent of patients reported pain to be of gradual onset without injury. A significantly higher proportion of female patients presented with gradual-onset pain (44 percent versus 28 percent). The study also showed a significantly greater proportion of males than females with work-related injuries (30 percent versus 13 percent).

The number of body regions involved was different between males and females. Among males, 46 percent had involvement of one body region; a greater proportion of females than males presented with involvement of two or more body regions (72 percent versus 54 percent).

A history of previous spine surgery was present in 35 percent of the patients. Surgery was more common among males (47 percent versus 27 percent).

Insurance status showed significant differences. A greater proportion of males than females were covered by Medicare with or without third-party insurance (39 percent versus 25 percent). Overall, 38 percent of patients were covered by third-party insurance, 31 percent were covered by Medicare with or without third-party supplemental insurance, 17 percent were covered by Medicare and Medicaid, and 14 percent were covered by Medicaid only. A total of 48 percent of patients were covered by Medicare, and 31 percent had Medicaid coverage.

Psychological characteristics

Psychological characteristics are illustrated in Table 2. Overall, depression, anxiety, and somatization disorder

Table 3. Prevalence of drug abuse and illicit drug use

	Male (n = 205)	Female (n = 295)	Total (N = 500)
Drug abuse			
Doctor shopping	9 (4.4 percent)	16 (5.4 percent)	25 (5 percent)
95 percent CI	(2 percent, 7 percent)	(3 percent, 8 percent)	(3 percent, 7 percent)
Trafficking	12 (6 percent)	9 (3 percent)	21 (4 percent)
95 percent CI	(3 percent, 9 percent)	(1 percent, 5 percent)	(2 percent, 6 percent)
Total opioid abuse	20 (10 percent)	26 (9 percent)	46 (9 percent)
95 percent CI	(6 percent, 14 percent)	(6 percent, 12 percent)	(7 percent, 12 percent)
Illicit drug use			
Marijuana	15 (7 percent)	39 (13 percent*)	54 (11 percent)
95 percent CI	(4 percent, 11 percent)	(9 percent, 17 percent)	(8 percent, 14 percent)
Cocaine	10 (5 percent)	14 (5 percent)	24 (4.8 percent)
95 percent CI	(2 percent, 8 percent)	(2 percent, 7 percent)	(3 percent, 7 percent)
Methamphetamine/amphetamines	2 (1 percent)	9 (3 percent)	11 (2 percent)
95 percent CI	(0 percent, 2 percent)	(1 percent, 5 percent)	(1 percent, 4 percent)
Total illicit drug use	25 (12 percent)	55 (19 percent)	80 (16 percent)
95 percent CI	(8 percent, 17 percent)	(14 percent, 23 percent)	(13 percent, 19 percent)

* Indicates a significant difference between male and female patients.

were documented in 59, 64, and 30 percent, respectively. A greater proportion of female than male patients were diagnosed with anxiety (69 percent versus 58 percent). There were no significant differences noted between male and female patients with depression or somatization disorder.

Opioid abuse/misuse and illicit drug use

A past history of illicit drug use was identified by self-report in 16 percent of patients. Table 3 illustrates drug abuse and illicit drug use characteristics. A total of 9 percent of patients were either "doctor shopping" or trafficking in opioids. While there were no significant differences noted between males and females, there was an insignificant trend among male patients for trafficking and among female patients for doctor shopping.

Table 3 also illustrates illicit drug use. Overall, the prevalence of illicit drug use was 16 percent—19 percent among females and 12 percent among males. Marijuana use was significantly higher in females than in males (13 percent versus 7 percent).

Drug abuse and illicit drug use characteristics by psychological status

Table 4 illustrates drug abuse and illicit drug use characteristics based on psychological diagnosis. There were no differences in current illicit drug use noted with regard to depression, anxiety, or somatization disorder. However, drug abuse was significantly higher in patients with depression than in those without (12 percent).

Table 5 shows drug abuse and illicit drug use characteristics based on psychological diagnosis and gender. Current illicit drug use was more frequent in women with depression than without (22 percent versus 14 percent) and more prevalent in depressed women than men (22 percent versus 12 percent). Prescription drug abuse was

Table 4. Drug abuse and illicit drug use characteristics based on psychological diagnosis						
	Depression		Anxiety		Somatization disorder	
	Yes (n = 296)	No (n = 204)	Yes (n = 319)	No (n = 181)	Yes (n = 151)	No (n = 349)
Current illicit drug use	53 (18 percent)	27 (13 percent)	18 (15 percent)	10 (12 percent)	13 (24 percent)	15 (10 percent)
Drug abuse	35 (12 percent*)	11 (5 percent)	35 (11 percent)	11 (6 percent)	16 (11 percent)	30 (9 percent)
* Indicates significant difference.						

also higher in women with depression (11 percent versus 4 percent). Current illicit drug use was highest in males with somatization disorder (22 percent versus 9 percent without).

DISCUSSION

This study showed a high prevalence of depression (59 percent), anxiety (64 percent), and somatization disorder (30 percent) in patients with chronic pain. Female pain patients presented with comorbid anxiety more often than male pain patients. Depression was shown to be a predictor of comorbid substance abuse, with 12 percent of depressed chronic pain patients showing substance abuse, versus 5 percent of pain patients without depression. Current illicit drug use was shown to be significantly higher in patients with depression than without and among females as compared to males. In this latter regard, subset analysis factoring for gender revealed that 22 percent of women with depression were using illicit drugs. Female patients with depression also showed a significantly higher prevalence of drug abuse (11 percent versus 4 percent). In contrast, male patients with somatization disorder showed a significantly higher prevalence of current illicit drug use compared to male patients without somatization disorder. These results are consistent with those of other studies that have shown an increased prevalence of depression, anxiety, somatization, and substance abuse/dependence disorders in chronic pain patients as compared to the general population.[4-28,36,61,62] Furthermore, given the correlation between chronic pain, patterns of emotional reactivity (to internal and external environmental stimuli evidenced in the presented psychopathologies), and substance abuse, the findings of the current study strengthen our previous work, which demonstrated that other biopsychosocial factors (such as pain subsequent to motor vehicle accidents, involvement of multiple anatomic regions, and past history of illicit drug use) are predictive for substance abuse in chronic pain patients.[38] Although our study did not demonstrate a clear association between current illicit drug use or drug abuse and anxiety or somatization disorder in women, this could be because the clinical testing instruments used were not sufficiently sensitive to detect such relationships. On the other hand, in regard to illicit drug use and abuse in the population of pain patients studied here, anxiety and somatization behaviors may have been nested within the features of depression.

To date, there is a relative paucity of valid measures that specifically address the predictive correlation between psychopathological variables and the potential for substance abuse in chronic pain patients. Of those in existence, most notable is a preliminary validation of the Opioid Risk Tool, in which Webster and Webster[29] identified five factors—family history of substance abuse, personal history of substance abuse, age of 45 years or younger, history of preadolescent sexual abuse, and the presence of particular psychological disorders (i.e., attention deficit disorder, obsessive-compulsive disorder, unipolar depression or bipolar disorder, or schizophrenia)—as potential risks for opioid abuse. Most other studies have not focused upon the role of psychological comorbidity in substance abuse in chronic pain patients; instead, they have tended to examine reactivity to and influence of environmental and circumstantial factors as possible risk predictors.

Chabal et al.[45] developed a prescription abuse checklist consisting of five criteria—overwhelming focus on opioid issues persisting beyond the third clinic treatment session; a persistent pattern of early refills; multiple telephone calls or office visits requesting more opioids; reports of consistent problems associated with the opioid prescription (including but not limited to lost, spilled, and/or stolen medications); and opiates obtained from multiple providers, emergency rooms, or illegal sources—that might be indicative of a high(er) substance abuse risk. Compton et al.[49] identified three items that were particularly viable in identifying misuse of opioids; these included belief of addiction by the patient, increasing analgesic dose or frequency, and route of administration preference. Passik et al.[50] developed a questionnaire that was employed among a small group of cancer and HIV patients to evaluate medication use, present and past

Table 5. Drug abuse and illicit drug use based on psychological diagnosis and gender							
		Depression		Anxiety		Somatization disorder	
		Yes	No	Yes	No	Yes	No
Current illicit drug use	Male (n = 205)	12 percent (13/111)	12 percent (12/94)	14 percent (17/119)	9 percent (8/86)	22 percent* (12/55)	9 percent (13/150)
	Female (n = 295)	22 percent** (40/185)	14 percent (15/110)	20 percent (41/200)	15 percent (14/95)	18 percent (17/96)	19 percent (38/199)
Drug abuse	Male (n = 205)	15 percent (14/111)	6 percent (6/94)	11 percent (13/119)	8 percent (7/86)	14 percent (8/55)	8 percent (12/150)
	Female (n = 295)	11 percent* (21/185)	4 percent (5/110)	11 percent (22/200)	4 percent (4/95)	8 percent (8/96)	9 percent (18/199)

* Indicates significant differences between women with or without depression and men with or without somatization disorder.
** Indicates significant differences between men and women and women with and without depression.

drug use, patients' beliefs about addiction risk, and aberrant drug-taking attitudes and behaviors.

Atluri and Sudarshan[54] developed a screening tool for detecting the risk of inappropriate prescription opioid use in chronic pain patients that identified six clinical criteria: patient focus on procuring opioids, opioid overuse, other substance use, nonfunctional exaggeration of pain, and unclear and/or improbable pain etiology. Manchikanti et al.[52] evaluated the instrument developed by Atluri and Sudarshan[54] and specifically identified three primary factors that appeared to reliably predict potential substance abuse: excessive opiate needs, deception or lying to obtain controlled substances, and doctor shopping. Holmes et al.[56] developed and introduced the Pain Medicine Questionnaire (PMQ) to assess the risk for opioid medication misuse in chronic pain patients. The PMQ is a 26-item questionnaire that evaluates various dimensions of chronic pain and attempts to isolate pain-related variables and factors that may suggest abuse liability. Savage[57] suggested that opioid addiction and/or its potential might be reflected or revealed through behaviors such as an unwillingness to taper opioids or try alternate pain treatments, decreased levels of function despite seemingly appropriate analgesia, and frequent requests for medication refills before renewal is due.

Clearly, the relationship between psychological state/condition (e.g., the presence or absence of psychopathology, as either directly indicated [as by Webster and Webster[29]] or implied through patterns of reactivity, behaviors, etc.), chronic pain, and the potential for substance abuse is strong, and we concur with the opinion raised in several studies that this reflects a biological basis for the comorbidity of certain psychopathologies (including substance abuse disorders) and chronic pain.[29,58-60,62] This thesis is fortified by the demonstrated co-involvement of several neuropharmacologic systems (e.g., serotonin, norepinephrine, dopamine, glutamate, gonadal steroids) and anatomical structures (namely the thalamo-cortico-limbic pathway) common to these disorders.[64,65]

It may be that the neural and/or glial chemistry, micro- and macrostructural anatomy of brain regions that are involved in mediating intero- and exteroceptive sensory (i.e., noxious) input, and the associative and emotive aspects of reinforcement and/or reward are disrupted or dysfunctional.[66] Underlying these neural (and possibly glial) phenotypic variations might be genetic variations that could potentially induce pleiotropic effects upon several substrates of neural and/or glial function (e.g., alterations in transmitter, receptor, and/or effector-signaling molecule synthesis or expression; expression of variant membrane constituents, including differentially sensitive ionic channels; etc.) to alter the pattern(s) of activity at brain loci that are involved in establishing "common neural bases" that predispose one to (or directly subserve) chronic pain, depression, somatization, and substance abuse.[67] Recent studies have shown that these loci include (but are not limited to) the parabrachial nucleus, amygdala, nucleus accumbens, and cingulate and frontal cortices as target zones of ascending sensory and internal associative/regulatory pathways.[68] The affective components operative in chronic pain (i.e., pain as protracted disease process and illness, affective pain) are akin to those of mood disorder and somatic sensitization.[69] Particular individuals are predisposed to the development of neural sensitization within these pathways as a consequence of overreactivity to insult and trauma, inflammation, or aberrant response to environmental input. The overexpression of neural substrates that subserve algesia or distress, together with a suppression or underexpression of pain-modulating, reinforcement, and reward substrates, might induce pathologic patterns of sensory hyperreactivity, altered cognitive processing and emotional responses, and loss of impulse control. In this way, persistent pain, psychopathology, and substance

abuse may be correlated and reflect related mechanistic processes.[70-73] As Koob and Le Moal[74] note, persistent pain involves "sensitization . . . that is defined by enhanced responsiveness to incoming signals . . . in the peripheral and central nervous system . . . . [A]ddiction also can be considered a type of chronic pain syndrome characterized by emotional pain, dysphoria . . . and interpersonal difficulties . . . . Drugs can be . . . self-medication for such pain."

Chromosomal quantitative trait loci (QTL) that affect neural phenotypes relevant to types of pain and certain psychopathologies including substance abuse have recently been identified.[75-77] These QTLs can either operate singly or multiply to affect particular phenotypes. Most surely, the phenotypes for pain, psychopathology, and substance abuse are multifactorial; therefore, it is likely that such QTLs establish a probabilistic basis for the (co)occurrence of these phenotypes along a continuum, while the actual expression of phenotypes as clinically relevant disorders is epigenetically influenced by the central nervous microenvironment and/or effects incurred by ongoing interactions between internal and external environments throughout the lifespan.[78,79] Variant patterns of these conditions appear to validate this possibility.

Tsuang et al.[80] showed that genetic influence in the abuse of marijuana, stimulants, and sedatives is shared across drugs. Thus, an abuser of one drug is more likely than nonabusers to go on to abuse a different category of drug. However, it has been shown that the genetic influence for heroin/opioid abuse is specific to heroin/opioids and is not shared with other drugs.[81,82] Thus, the high probability of genetic influence on opioid abuse fortifies the repeated finding that familial and personal history of opioid drug abuse is heavily weighed in risk analyses of opioid misuse.[29] Taken together, such findings suggest that genotypic variants might predispose either 1) a "generalized" pattern of diathesis, in which neural substrates of environmental sensitivity, responsivity, reinforcement, and reward are altered to affect interpretive/ associative aspects of bodily sensations (including discomfort and pain), appetitive drives, and emotionality; or 2) more "specific" diatheses, in which particular neural phenotypes are affected which directly correlate to certain forms of pain and/or psychopathology and substance dependency.[83,84] Albeit speculative, it is tempting to postulate that genetic alteration in the expression of opioid, glutamate, and/or GABAergic receptors (or receptor-linked mechanisms) and/or cation-channel expression might underlie sensitivity to pain, development of particular types of pain (e.g., neuropathic syndromes), the constellation of somatic and cognitive features found in forms of depression and somatization disorder, and decreased viability of opioid-dependent neuromodulation,

therefore impacting predisposition to escalative misuse of opioids.

If we consider that these comorbidities may represent environmentally dependent, differential expression of neural and behavioral phenotypes that are established by a relatively confined set of genomic influences, then we may view chronic pain as a spectrum disorder that may co-manifest (other) neuro- and psychopathological effects/conditions.[85,86] Working from the concept that chronic pain and psychological disorders may be correlated along a neuropathological continuum, it becomes important to recognize that 1) these disorders represent underlying genomic diatheses, and the expression of phenotypic substrates is differentially dependent upon particular interactions with internal and external environmental factors; 2) it is possible—and likely—that such genetic-environmental covariance sustains that comorbidity; 3) this covariance is equally likely on several dimensions of cause and effect; and 4) these effects may be manifested in the co-terminal expression of chronic pain and mood, somatization, and substance abuse disorders. Thus, it may be that (clinically relevant) depressive and somatization signs and symptoms are viable psychological endophenotypes that have predictive value for the substance abuse potential of chronic pain patients, particularly if viewed alongside other identified biopsychosocial risk factors.

To be sure, these conclusions are highly speculative, and multiple issues may be raised regarding methodology and the relevance and relativity of definitions of opioid abuse, illicit drug use, doctor shopping, and drug trafficking. We posit that the sampling methodology we used was appropriate for the type of evaluation, and that the methods of psychological evaluation were also appropriate to context, setting, and applicability to interventional pain management. In this latter regard, it has been shown that the psychological diagnostic impressions achieved by utilizing DSM-IV-TR criteria were superior to self-report questionnaires or loosely structured interviews.[4,11] In the present study, we have included patients who have been characterized with depressive features by evaluation of past psychological history, DSM-based questionnaire, and use of the MCMI; thus, the number of patients presenting with such operationally defined depression may be higher than in our previous work. However, we believe that this multifocal assessment approach has higher sensitivity and therefore more reliably captured depression within this patient population.

The major purpose of this study was to evaluate and address the predictive value of multiple risk factors for drug abuse and illicit drug use in chronic pain patients. Therefore, the present study is an extension of our previous work, which identified physical factors predisposing subjects to substance abuse.[38] By now evaluating and

identifying psychological factors, we move toward a biopsychosocial approach to assessment, upon which a more comprehensive scope and trajectory of care might be conceived and implemented.

Clearly, our knowledge of pain, psychological conditions, and substance abuse influence the epistemic basis of both medical practice and the ethics that guide such care.[87,88] An understanding of the neurobiology of these disorders allows us to view them as pathological processes ascribed to a disease model. But this remains a double-edged sword, for while we adopt an integrative-approach disease model of assessment, we often continue to adhere to an older, more Cartesian, dualistic (body versus mind) approach to care, which can foster clinical disregard of psychological disorders—including substance abuse—as being "only in the mind." However, nesting neurobiology within a biopsychosocial framework allows for insight into the mechanisms and effects of genetic, phenotypic, and environmental interactions in the expression of disease and manifestation of illness, and it equally compels the use of a biopsychosocial approach to treatment of these disorders.[89-91] In sum, the better we understand how genetics and neurobiology affect individual patients, the better we will be able to adapt clinical practice to meet the complex individual medical needs of each person in pain.

CONCLUSION

This study demonstrated that 1) the presence of psychological features of depression and somatization may be endophenotypes of substance abuse diathesis in chronic pain patients, and 2) these psychological features are reasonable predictors of substance abuse in chronic pain patients. These conclusions are based upon both the quantitative analyses of specific data and reflection upon the most contemporary understanding of the neurogenetics of these pathologies, hypothesized herein to be components of a neuropathological spectrum disorder. This provides a basis for both theoretical and predictive contextual knowledge, and we advocate that such knowledge should inform and sustain the ethical practice of pain medicine.[92,93] A deepened understanding of pain, psychopathology, and addiction allows for an enhanced ability to treat, heal, and care as necessary. Ongoing work by our group is dedicated to continued research to advance this approach.

ACKNOWLEDGMENTS

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