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Sex differences among opioid-abusing chronic pain patients in a clinical trial

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Abstract

Background—The characteristics of patients with co-occurring chronic pain and prescription opioid abuse have not been well described, and even less is known about differences between men and women in this population.

Objectives—This study evaluated sex differences in the demographic, diagnostic, and behavioral attributes of patients with chronic pain and opioid abuse.

Methods—Data were collected via self-report and semi-structured clinical interviews from 162 patients (120 M, 42 W) who screened for a study investigating the abuse liability of prescription opioids.

Results—There were no differences between males and females in age, race, education, marital status or employment status. Participants had used prescription opioids for 5.4 ± 6.7 years. The majority of participants (60%) had low back pain in addition to opioid dependence as defined by

Disclosure

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the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). More women reported more arthritic pain than men, but otherwise there were no differences in types of pain. Pain exerted a greater effect in women on mood, walking ability, and social relations. Men reported more of certain aberrant behaviors including abuse of alcohol or illicit drugs, unauthorized dose increases, contact with street culture, and being arrested by police. Women were more depressed than men.

Conclusions—The demographic profile of opioid-abusing chronic pain patients presenting for treatment in a clinical trial was similar between sexes; however, some important differences were observed. Women reported more psychiatric co-morbidity and endorsed greater pain-related physical and social impairment. Men reported more aberrant behaviors. These differences suggest that men with chronic pain and opioid abuse/dependence may benefit by closer monitoring of aberrant behaviors while women may benefit from closer attention paid to physical and psychological effects of pain.

Keywords

opioid abuse; chronic pain; sex differences

INTRODUCTION

The substantial rise in opioid prescribing over the past decade has been accompanied by dramatic rises in the incidence of prescription opioid abuse (Gallagher and Rosenthal, 2008; Manchikanti et al., 2010). And yet, little is known about patient populations with concurrent chronic pain and opioid abuse. For instance, few studies have examined the differences in clinical presentation between men and women with this comorbidity. While the treatment approach for the management of chronic pain is currently the same for women as for men, sex differences exist in terms of pain manifestation, coping, and aberrant behaviors. Understanding sex-based differences in patients' presentation with chronic pain syndromes, as well as their responses to opioid analgesics, holds the potential for improving clinical assessment, tailoring pain management strategies, and minimizing abuse liability.

Sex-based differences are found in the prevalence of certain pain conditions, as well as the emotional sequelae from chronic pain. Women are at greater risk for developing multiple concurrent chronic pain conditions as well as inflammatory-related disorders (Manson, 2010). Women also tend to tolerate greater pain severity in an attempt to maintain their role functioning in the family (Darnell and Stacey, 2012).

Strong evidence exists for sex differences in sensitivity to pain and response to analysics (Manson, 2010). In clinical settings, women tend to experience greater negative emotions from pain than men (Darnell and Stacey, 2012). Further, women have been found to report greater negative subjective effects following morphine administration in a laboratory setting (Comer et al., 2010).

In addition, men and women differ in the risk factors associated with prescription opioid abuse. Women have different coping responses to pain than do men, and misuse opioids in distinct ways. Among opioid-dependent patients, women endorse more depression and

anxiety than men (Munce and Stewart, 2007), as well as more current and past medical problems (Back et al., 2011). Women are more likely to use prescription opioids to cope with interpersonal stress, and to use opioids upon first awakening in the morning (Back et al., 2011). Women (but not men) with solicitous spouses are more likely to use greater amounts of opioids (Fillingim et al., 2003). Whereas women are more likely to abuse prescription opioids because of affective distress, men tend to misuse opioids because of legal and problematic behavioral issues (Jamison et al., 2010).

Pharmacy records in the United States demonstrate that women are more likely to be prescribed opioids than men, and are more likely to take higher daily doses (Williams et al., 2008; Campbell et al., 2010). Women being prescribed opioids in chronic pain clinics are more prone to taking a greater number of medications (opioid and nonopioid) compared to men (Darnell and Stacey, 2012), a practice that exposes them to a higher risk for drug-drug interactions, additive side effects, and possible overdose. In the past 15 years, opioid-related overdoses leading to hospitalization have increased for women but not for men (Coben et al., 2010). This trend was also recently reported in an analysis by the CDC, which noted an increase in the percentage in deaths from opioid pain reliever overdose among women compared to men since 1999 (Mack and Paulozzi, 2013).

Some sex differences in patterns of taking prescribed and non-prescribed opioids have been identified. Women are twice as likely as men to receive prescriptions from 5 or more clinicians in the prior year (Hall et al., 2008). Among treatment-seeking opioid abusers, women are more likely than men to report receiving opioids through a legitimate prescription (Cicero et al., 2008). By contrast, men are more likely to obtain prescription opioids for free from family or friends, and are more likely to purchase them from a dealer (Back et al., 2010). Men are also significantly more likely to alter the route of administration by inhaling and injecting prescription opioids, compared to women (Back et al., 2011).

Men and women also differ with respect to concurrent illicit drug use patterns. In a multisite effectiveness trial of opioid-dependent individuals, more women tested positive for amphetamine, methamphetamine, and phencyclidine, whereas more men tested positive for methadone and marijuana (Back et al., 2011). While polysubstance use and drug treatment underutilization are common among men and women, significantly fewer women than men have received alcohol or drug abuse treatment (Back et al., 2010).

Chronic pain has been found to be associated with psychiatric disorders and physical impairment in studies based both on clinical samples and epidemiological surveys. Epidemiologic studies have shown that psychological comorbidity negatively affects the prognosis and course of chronic pain (Tunks et al., 2008), and that there is a high prevalence of co-occurring depression in chronic pain samples (Miller and Cano, 2009). Back pain, one of the most common chronic pain conditions, is significantly associated with major depression, with some studies reporting prevalence rates as high as 59% among chronic pain patients (Cheour et al., 2008; Subramanium et al., 2013). There is a high association of increased physical impairment, greater service utilization, and poorer health among chronic pain patients receiving opioids who have a history of mental health disorders, including generalized anxiety disorder (GAD) and major depression (Turk and Okifuji, 1997).

Psychiatric factors, including mood disorders, have also been shown to be a risk factor for aberrant drug-related behavior among patients prescribed opioids for chronic pain (Wasan et al., 2007). Higher opioid doses are often prescribed to patients who report greater pain severity and in those who report higher levels of opioid-related psychosocial problems (Merrill et al., 2012). Findings from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) support the fact that individuals with bipolar disorder or GAD have a general vulnerability to nonmedical opioid use, and there is evidence for a 'self-medication' model leading to dependence in this patient population with psychiatric comorbidity (Martins et al., 2009). Further, the NESARC data also showed greater comorbidity between mood and anxiety and drug use disorders among women than men (Conway et al., 2006).

The present study is a secondary analysis of sex differences in a sample of opioid-abusing chronic pain patients who presented for a treatment study for chronic pain. The effect of sex upon assessments of pain ratings, mood, and aberrant behaviors assessed during screening was examined. By understanding sex differences related to pain response and patterns of misuse, clinicians may be able to identify sex-specific risk factors that can better guide pain management, and help to prevent misuse.

METHODS

Data were collected from patients who screened for an IRB-approved 7-week inpatient, 12-week outpatient study investigating the abuse liability of oxycodone under conditions of buprenorphine/naloxone (bup/nx) maintenance, as well as the utility of bup/nx for treating patients diagnosed with concurrent pain and opioid abuse. Prior papers from this dataset analyzed the effects of bup/nx and oxycodone on pain, opioid withdrawal symptoms, and abuse liability among enrolled participants in this study (Jones et al., 2011; Roux et al., 2013). The sample for this paper consisted of screening participants who met criteria for opioid abuse/dependence for prescription opioids with chronic pain (duration of 6 months or longer), regardless of whether they subsequently enrolled in the treatment study.

Recruitment Methods and Study Procedures

Participants for this research study were recruited through the Substance Use Research Center, as well as advertisements in local newspapers, radio, and community bulletin boards. Participants who responded to advertisements came for a series of screening appointments at the New York State Psychiatric Institute during which they were to complete a set of questionnaires and meet with a study physician for a physical exam and psychiatric evaluation.

As part of the screening process, we administered the following questionnaires: Brief Pain Inventory (BPI) (Cleeland and Ryan, 1994), Pain Disability Questionnaire (PDQ) (Anagnostis et al., 2004), Hamilton Depression Scale (HAM-D) (Hamilton, 1980), Pain Assessment and Documentation Tool (PADT) (Passik et al., 2004), and the Medications Belief Survey (Horne et al., 1999). The BPI is an 11-item questionnaire designed to evaluate the intensity of, and impairment caused by, pain. The Ham-D is a 25-item scale assessing the range of symptoms most frequently observed in patients with Major Depression. The

PADT is a 41-item clinical tool which measures four domains (pain relief, patient functioning, adverse events, drug-related behaviors) of outcome in pain management. The Medications Belief survey assesses beliefs about the necessity of medication and concerns about it.

All questionnaires were self-administered, with the exception of the clinician-administered PAD-T and Hamilton-D. We specifically asked about chronic pain that is not related to potential opioid withdrawal-related pain during the medical interview. Locations of pain indicated on the diagram on the BPI were confirmed during the physical examination, if musculoskeletal pain was reported.

Inclusion/Exclusion Criteria

Patients in this screening sample were male or non-pregnant/non-lactating female, and seeking treatment for their chronic, non-malignant pain condition. In addition to having chronic pain, patients also met DSM-IV criteria for opioid abuse and prescription opioid physical dependence. Study physicians contacted participants' medical doctors to confirm opioid prescriptions and the diagnosis of chronic pain.

Concurrent heroin use was allowed, however, primary heroin dependence was exclusionary for study participation. Some screens were taking additional non-prescribed opioid medication, in addition to their prescribed opioid. Dependence on drugs other than prescription opioids (excluding nicotine and caffeine) led to exclusion from enrollment in the treatment study, as did abnormal medical findings, or unstable psychiatric conditions.

Prescribed benzodiazepine use was exclusionary. Individuals with urine toxicologies that were positive for benzodiazepines were considered to be using them illicitly. Patients with positive benzodiazepine urine screens were included in the present analyses, yet ultimately excluded from the primary study.

Participants were asked to provide a urine sample for drug testing at every screening visit; urine toxicology tests were collected on 148 of the 162 screening participants. A positive toxicology on urine dipstick testing for opiates included morphine, hydrocodone, hydromorphone, codeine, and heroin. Tramadol did not result in a positive opiate result. However, there was a cross-reaction on the urine dipstick, such that a PCP-positive test-result occasionally occurred with reported tramadol use. A urine toxicology result that was not consistent with self-reported opioid use led to exclusion from the primary study.

DATA ANALYSES

Data were initially summarized descriptively with percentages, means, and standard deviations. A number of missing data points across instruments was discovered and it was clarified that these missing data reflect removal from, or dropping out of, the screening process. As such, total number of patients who completed each instrument varied. Differences between the patients on continuous measures were examined with t-tests. If unequal variance was present, then the adjusted t and degrees of freedom are reported. Differences between patient groups on categorical variables were examined with chi-square

analyses. Analyses were considered significant at the p<.05 level. Given the paucity of studies examining patients with chronic pain and opioid abuse/dependence, findings at he p<.10 significance level were also included for descriptive purposes. Analyses were conducted with SPSS (IBM, version 20).

RESULTS

Demographics

There were 191 individuals who attended at least one screening visit for this study. Twentynine individuals were excluded because they were not abusing or were not dependent on opioids. Therefore the final sample reported here is n=162 (120 Males, 42 Females). Demographics of the sample are presented in Table 1, and reveal no differences between males and females in age, race, education, marital status or employment status.

Mood

With regard to mood, prior studies have shown that women with chronic pain typically carry greater psychiatric co-morbidity than men (Conway et al., 2006). The present results are consistent with these findings. Although there were no sex differences in percentage of the sample with MDD, anxiety or panic disorder diagnoses (Table 1), total depression scores on the HAM-D-25 assessment were significantly different between men and women (men M=13.95, SD=7.7, women M=19.05 SD=9.5), t (77)= -2.40, p=.019, suggesting greater levels of depression in women.

Pain Demographics

Table 2 characterizes the pain demographics of the sample. On average, patients reported experiencing chronic pain for 9 years, and using opioids for about 5.5 years. The average daily dose of prescription opioids was $159.9 (\pm 165.1)$ mg morphine equivalents for women, and $179.1 (\pm 224.3)$ mg for men. The majority of participants had low back pain (60%), or other musculoskeletal pain (40.3%). Also reported were arthritic (16.2%) and other pain (16.3%) (e.g. spinal stenosis, multiple sclerosis, chronic pelvic pain, neurofibromatosis). More women reported arthritic pain than men (p<.01).

Urine Toxicology Results

Table 3 presents the urine toxicology data. Concomitant illicit drug use was determined by self-report and urine toxicology. Slightly more than half of the sample gave a urine sample that was positive for opiates (morphine, hydrocodone, hydromorphone, codeine, or heroin). About 49% of individuals reported the use of multiple types of opioids during screening. The other primary drug used was oxycodone (39%). The percentage of individuals self-reporting any current heroin use was 13.8%. Additional findings from urine toxicology revealed 27% cocaine-positive urines, 18% benzodiazepine-positive urines, and 14% cannabinoid-positive urines.

Pain Ratings

Table 4 presents the pain ratings captured with the Brief Pain Inventory (BPI). Women and men had comparable levels of average daily pain, however, women reported somewhat worse pain in the last week than did men. Women also reported greater effects of pain on mood, walking ability, and relations with other people.

As a global assessment of pain tolerance, participants were specifically asked, "What level of pain could you function with on a daily basis?" Answers ranged from 0 (no pain) to 10 (worst pain imaginable; 11-point scale). Women reported a mean score of 4.81 (SD=2.71), and men reported a mean score of 5.20 (SD=2.48), which is a non-significant difference.

The upper half of Table 5 presents data from the Pain Disability Questionnaire (PDQ). Women reported more pain-related physical limitations, such as walking short distances and climbing stairs more slowly. Women also reported more interference with specific activities of daily living, such as sleeping (difficult to turn in bed because of pain). There were no items for which men reported significantly greater endorsements.

Aberrant Behaviors

In contrast, Table 5 (lower half) reveals that men were more likely than women to have engaged in certain aberrant behaviors, such as contact with street culture or being arrested by the police than women. A somewhat higher percentage of men reported abusing alcohol or illicit drugs, $\chi^2(1)=3.19$, p=.07 and increased medication doses without authorization, $\chi^2(1)=3.15$, p=.08. Women were most likely to endorse negative mood changes as a result of their pain and to appear intoxicated during the assessment when compared to men (data not shown).

In summary, among chronic pain patients with a history of concurrent opioid abuse, women reported significantly more physical limitations and psychological changes (e.g. negative emotional states) associated with pain. In contrast, men tended to endorse certain external aberrant behaviors (e.g. increasing dose of their medication without authorization, contact with street culture) with a greater frequency than women.

DISCUSSION

The demographic profile of opioid-abusing chronic pain patients presenting for treatment in our clinical trial was similar between men and women. There were no significant differences between the sexes with respect to age, ethnicity, marital status, years of education, and employment status. Similarly, there were no significant differences between men and women in terms of examined clinical features, including level of daily opioid use, or mean duration of opioid use. Women had more arthritic pain than men.

However, there were several sex differences in the impact of pain on daily functioning, as well as psychiatric features associated with the pain condition. Women reported more psychiatric co-morbidity with higher baseline depression (HAM-D) scores compared to men. Women also reported higher levels of worst pain (in the last week), and greater physical and social impairments from pain, whereas men endorsed more specific aberrant

behaviors, such as increasing their dose without authorization. These differences are consistent with prior reports of features of chronic pain specific to men and women (Fillingim et al., 2003; Chenot et al., 2008; Jamison et al., 2010).

With regard to aberrant behaviors, differential patterns of endorsement did emerge. A greater proportion of men reported abuse of alcohol or illicit drugs, and had a history of contact with street culture or arrests by police. They were also more likely to increase opioid dose without authorization, or to become increasingly unkempt or impaired. As a consequence of unauthorized dose escalation, men may engage in drug-seeking behavior from other sources, including emergency rooms, friends, or street dealers.

Compared to men, women endorsed a greater variety of aberrant behaviors on the PADT (although non-significantly so) including more subtle features such as negative mood change and appearing intoxicated. These results may suggest a heightened sensitivity to opioid effects, including adverse effects among women. Consequently, it appears that women may be less likely to achieve successful pain management with opioids and suffer more physical limitations. It may thus be more difficult for pain management clinicians to accurately assess opioid-related impairment in women using standard pain instruments.

These findings demonstrate the need to integrate psychiatric and pharmacological modalities in the management of chronic pain, as well as concurrent chronic pain and opioid abuse. Clinicians treating chronic pain should screen for mood and substance use disorders at baseline (prior to initiation of opioid therapy), and provide necessary treatment or referrals for those exhibiting characteristics consistent with abuse of opioids. Tools that capture aberrant behaviors (such as the PADT) in combination with those that are sensitive to pain interference and activities of daily living (BPI) should be considered. Inquiring directly about mood, sedation, and declining interpersonal relations may yield valuable evidence for the presence of prescription opioid abuse.

In particular, urine drug testing results should be consistent with opioids prescribed. In addition to ensuring that prescribed opioids are present in the urine, toxicology results can also detect the presence of non-prescribed opioids, or even illicit drugs. It has been our experience that urine toxicologies are an underutilized, yet extremely valuable tool in the management of chronic pain. Combining urine toxicology tests with treatment contracts that underscore consequences of inconsistent urine toxicology results or aberrant behaviors represents a powerful strategy to enable treatment success. Further, providing a wider range of non-opioid treatments, addressing side effects, understanding pharmacologic limitations, and encouraging better coping skills may also be effective strategies for clinicians working with this population.

The influence of sex differences on the impact of pain and the manifestation of aberrant behaviors identified in this study highlights the importance of approaching the management of chronic pain through the use of more individually tailored strategies. Greater awareness of sex-specific clinical profiles may allow clinicians to detect negative consequences of pain syndromes and opioid analgesics early in treatment. Our findings suggest that aberrant behaviors in women may be more covert, such as experiencing negative mood changes.

Women also endorsed more physical limitations, and greater interference of pain on certain activities of daily living. Men reported more overt behaviors, including arrests from police, and being involved with street culture. Recognition of the distinct characteristics of treatment-seeking opioid-dependent men and women could help guide changes in pain management before opioid abuse behaviors begin or escalate.

When considering these findings, limitations to the study must also be mentioned. Specifically, there were more men than women, which contributed to the need to correct a number of the comparisons for unequal variance. This may have resulted from the fact that the study for which participants were screening had an intensive inpatient requirement (7 weeks). Thus, this sample may be somewhat biased and not be fully representative of clinical treatment populations. Nevertheless, given the paucity of data describing patients with both chronic pain and opioid abuse or dependence, it is still informative to consider these findings.

CONCLUSIONS

The present findings highlight future directions. There is a need for instruments that are more specific to the issues that arise in the opioid-abusing chronic pain patient population. For instance, the development of opioid risk screening tools that focus on psychological effects and quality of life measures would be a valuable addition to those already in existence. These data support the notion that the comprehension of subtle sex differences may be useful in the development of such instruments.

To conclude, more and larger studies including demographic characteristics and clinical outcome measures in patients with chronic pain and opioid abuse may identify further differences between men and women. These studies are greatly needed, and could offer guidelines for a newer approach toward individualized treatment of comorbid pain and opioid dependence that incorporates sex-specific measures. The data presented here contribute to this effort.

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Table 1

Demographic Profile

	Gender	Gender	
	Male (120)	Female (42)	
Age in Years (SD)	46.7 (8.8)	48.4 (10.0)	47.1 (9.1)
Race			
Hispanic	17.6%	22.0%	18.8%
Black/ AA	31.9%	46.3%	35.6%
White	45.4%	31.7%	41.9%
Native American	1.7%	0.0%	1.3%
Other	3.4%	0.0%	2.5%
Education in Years (SD)	12.9 (2.0)	13.1 (2.1)	12.9 (2.0)
Less than High School	9.8%	15.7%	11.5%
High School	49.5%	34.4%	45.9%
Some College	24.7%	37.5%	27.7
College	16.0%	12.5%	14.9%
Marital Status			
Single	50.9%	48.6%	50.2%
Married	19.8%	24.3%	20.9%
Separated	10.3%	2.7%	8.5%
Divorced	14.7%	14.7% 21.6%	
Widowed	4.3%	2.7%	3.9%
Employment Status			
Full/ Part-Time	15.8%	5.3%	13.2%
Unemployed	39.4%	39.5%	39.5%
Retired	2.6%	10.5%	4.6%
Disabled	33.3%	26.3%	31.6%
Public Assistance	5.3%	10.5%	6.6%
Other	3.5%	7.9%	4.6%

Note: There were no differences between Males and Females

Anxiety Disorders (e.g., GAD, panic disorder, OCD)

Current or lifetime MDD or Depression NOS

Bipolar Disorder

19.8 %

11.4%

7.0%

34.6%

32.0%

11.1%

23.6%

16.7%

8.1%

Table 2

Pain Demographics

Pain Demographics

	Gender		
	Male (108)	Female (40)	Total (148)
Mean years of Pain (SD)	8.12 (7.2)	11.03 (11.8)	8.87 (8.7)
Mean years of opioid use (SD)	4.86 (5.1)	6.90 (9.8)	5.40 (6.7)
Mean daily morphine equivalence of prescribed opioids (SD)	179.1 (224.3)	159.9 (165.1)	173.9 (209.6)
Types Of Pain *			
Lower Back Pain	61.9%	51.2%	59.1%
Arthritic Pain I	10.6%	31.7%	16.2%
Other Musculoskeletal	42.5%	34.1%	40.3%
Other	13.4%	24.4%	16.3%

Notes

^{*} Not mutually exclusive

 $^{^{}I}$ Women reported a higher proportion of Arthritic Pain, $X^{2}(1) = 9.83$, p < .01

Table 3
Urine Toxicology Results: Percent positive for each drug at screening

Substance	Gender		
	Male (91)	Female (34)	Total (125)
Opiate*	53.8%	52.9%	53.6%
Oxycodone	37.4%	44.1%	39.2%
Cocaine	27.5%	26.5%	27.2%
Benzodiazepine	18.7%	17.6%	18.4%
Cannabinoids	16.5%	8.8%	14.4%
Methadone	11.0%	20.6%	13.6%
PCP	3.3%	2.9%	3.2%
Barbiturates	0%	5.0%	1.3%
Amphetamines	0%	2.9%	0.8%
Opioid combinations (based on self-report)			48.8%

^{*} Opiate positive urines included morphine, hydrocodone, hydromorphone, codeine, and heroin. Tramadol did not result in an opiate positive urine, but was occasionally positive for PCP.

Table 4

Pain Ratings

Brief Pain Inventory

	Gender			
	Male (n=112)	Female (n=36)		
	M (SD)	M(SD)	t	df
Average pain in the last week	6.48 (1.78)	6.78 (2.02)	0.86	145
Worst pain in the last week	7.72 (1.78)	8.31 (1.64)	1.74	146
General activity	6.54 (2.34)	7.31 (2.45)	1.69	144
Mood	5.80 (2.61)	7.14 (2.61)	2.68*	142
Walking ability	5.66 (2.30)	7.19 (2.68)	2.73*	142
Normal work	6.38 (2.95)	7.19 (2.88)	1.45	142
Relations with other people	4.92 (2.89)	6.11 (2.54)	2.21*	143
Sleep	6.43 (2.78)	7.28 (2.45)	1.64	142
Enjoyment of life	6.61 (2.69)	7.03 (2.72)	0.81	143

Note

The Brief Pain Inventory pain ratings range from 0-10, where 0 is "No Pain" and 10 is "Pain as Bad as You Can Imagine" Other questions ask about pain interference: "0" refers to "Does Not Interfere" and "10" refers to "Completely Interferes"

 $^{^{+}}$ = p < .10

p < .05.

Table 5
Pain-related Physical Limitations and Aberrant Behaviors

	Gender			
	% Male	% Female	X ² (1)	n
PDQ: Endorsement of pain-related physical limitations				
I find it difficult to turn in bed because of my pain	58.8	88.5	7.48*	94
I only walk short distances because of my pain	67.1	84.6	2.86	96
I go up stairs slowly because of my pain	84.3	100.0	4.61*	96
PADT: Reported behaviors to doctor by gender				
Abusing alcohol or illicit drugs	17.2%	0.0%	3.19 ⁺	74
Increased dose without authorization	91.4%	75.0%	3.15	74
Contact with street culture	58.6%	25.0%	5.67*	74
Arrested by police	22.4%	0.0%	4.35*	74

Note

 $^{^{+}}$ = p < .10

p < .05.