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Problematic Prescription Opioid Use in an HIV-infected Cohort: the Importance of Universal Toxicology Testing

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Abstract

Background—Providers treating chronic pain must attempt to relieve suffering, while minimizing problematic prescription opioid use, including addiction and diversion. Previously described risk factors for problematic use include: history of substance use, younger age, male sex, psychiatric comorbidity, and lower education level.

Methods—We examined these risk factors in HIV-infected individuals, using cross-sectional and longitudinal data from the Manhattan HIV Brain Bank. Problematic use was defined as illicit substance use (documented by urine toxicology or structured psychiatric interview) while receiving prescription opioids.

Results—Among 173 participants prescribed opioids, 62% had problematic use, the majority of which was discovered by urine toxicology. Problematic use was associated with past substance use, current psychiatric disorder, and poorer adherence to antiretrovirals. However when participants without problematic use at baseline were followed longitudinally, these factors were not predictive. Furthermore the cumulative incidence of problematic use behaviors was no greater than in a similar group of participants who were not prescribed opioids.

Conclusions—Problematic prescription opioid use is common among HIV-infected individuals and is associated with history of substance use, current psychiatric disorder, and poor adherence to antiretrovirals. However these factors do not predict future problematic use in those who are not currently using illicit substances, and the prescription of an opioid does not appear to predispose patients toward a future substance use disorder. Rather than attempting to assess risk for problematic prescription opioid use in HIV-infected individuals, we recommend baseline and follow-up urine toxicology.

Keywords

HIV; aberrant; opioid; misuse; chronic pain

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Introduction

The use of opioids for the treatment of chronic pain in non-cancer populations is a controversial subject. This lack of consensus arises from the lack of adequate data supporting the safety and efficacy of opioids in non-cancer pain, and also from legal and ethical concerns surrounding the harm that may be caused by abuse and diversion of prescription opioids into the community. Thus the clinician faced with a chronic pain patient, who still appears to be suffering despite non-opioid analgesia, may be conflicted about whether to prescribe opioids. Under-treatment of pain has been documented in the medical literature and publicized in the lay press.¹ Efforts to improve the treatment of pain led to the numeric pain score being adopted as the “fifth vital sign”.² Adequate treatment of pain has been referred to as a “moral imperative”.^{1, 2} Patients claiming that their pain was not adequately addressed have won malpractice suits.³ However it is increasingly clear that an overly liberal approach to the prescription of opioids is not desirable either. There has been a dramatic rise in prescription opioid abuse and death due to overdose.⁴ Clinicians have been convicted on criminal charges for over-prescription of opioids.⁵

In light of these mixed messages, there is great interest in determining the most appropriate and safe opioid prescribing practices. To this end, it is desirable to define what constitutes a poor outcome of treatment with opioids. Possible poor outcomes include lack of efficacy, side effects, development of addiction, and diversion of opiates. The former two outcomes are similar to those that must be considered for any medication, while the latter two are more specific to substances with abuse potential.

A body of literature beginning in the late 1990s began addressing addiction and diversion behaviors in patients prescribed opioids using the terms problematic opioid use, aberrant opioid use, and opioid misuse.^{6–8} Although there is not a single gold standard definition of problematic use, a simple and broad conceptual definition is: use of the prescription opioid in a manner that deviates from the provider's instructions. This includes abuse, misuse and diversion. Since these are not often directly observable behaviors, more specific clinical features have been described including: unexpected toxicology results, frequent requests for dose increases, failure to adhere to concurrently recommended treatments, frequently reported loss of prescriptions or medications, tampering with prescriptions, prescriptions obtained from multiple providers (including emergency rooms), and missed and/or extra follow-up visits.⁹

Researchers have sought to determine risk factors for problematic use and to develop tools to predict it. However there are significant methodological hurdles, as described by Turk and colleagues in a systematic review of the literature published in 2008.⁶ One of the main difficulties is choosing a valid outcome measure. The researcher is unlikely to be able to objectively document problematic behaviors such as tampering with prescriptions or opioid diversion. The available alternatives include patient self-report, provider report and urine toxicology screening. Each has significant limitations. Patients have incentive to conceal substance misuse and have been shown to do so.¹⁰ Providers have no way of truly knowing what their patients do with their medications. Urine toxicology has the advantage of objectivity, but gives a circumscribed picture.

Despite these difficulties certain patient characteristics have been associated with problematic use in one or more studies and are generally considered to be possible risk factors. The most consistent and perhaps most obvious is a past history of drug or alcohol abuse^{11–13}. Other potential risk factors that have been studied include: younger age,^{13, 14} male sex,^{13, 15, 16} psychiatric comorbidity,^{11, 12, 14, 15, 17, 18} lower education level,¹⁸ family history of substance use,^{11, 15} and history of sexual abuse.¹⁸

These potential risk factors pose a dilemma for providers treating HIV-infected individuals, because many of them are so common in certain HIV populations as to make meaningful risk stratification impossible. Yet pain is also extremely common among HIV-infected individuals. In a recent survey of HIV primary care practices, providers reported on average that 28% of their patients had chronic pain.¹⁹ Recent patient-based studies have reported prevalence of pain at above 50%.^{20–22} Prescription of opioids to HIV-infected individuals is also higher than in the general population.²³

A few publications have begun to examine problematic use specifically in HIV-infected individuals.^{24–26} Hansen and colleagues studied a group of marginally housed or homeless HIV-infected adults in San Francisco and found a high prevalence of problematic use, as assessed by an affirmative answer to at least one of 20 items queried using an audio computer-assisted self-interview.²⁵ Tsao and colleagues utilized data from the HIV cost and services utilization study (HCSUS) and found greater opioid misuse among patients with histories of drug problems.²⁶ Both variables were defined based on responses to questionnaire items developed for HCSUS. However a study of a broad range of risk factors for problematic prescription opioid use in HIV-infected individuals has not been performed. In this study we sought to determine whether the risk factors described among chronic pain patients would also be associated with problematic use in HIV-infected individuals, using both urine toxicology and psychiatric interview to define outcomes. In addition we sought to examine the role of some factors specifically pertinent to HIV namely: adherence to antiretrovirals (ARVs), CD4+ count, plasma HIV viral load (VL) and burden of co-morbid illnesses.

Methods

Participants and study procedures

Data were obtained from the Manhattan HIV Brain Bank (MHBB), an ongoing prospective cohort study established in 1998 to provide a resource of nervous system tissues from HIV-infected donors who undergo comprehensive, longitudinal, ante-mortem evaluation. The MHBB is a member of a four site consortium, the National NeuroAIDS Tissue Consortium. The primary enrollment criterion for the MHBB is willingness to participate in organ donation at the time of death. Other criteria were designed to target patients with advanced disease (e.g. hemoglobin less than 10 g/dL, CD4 count less than 50, opportunistic infections) or other illness refractory to therapy (congestive heart failure, end stage liver disease). Following enrollment, participants are evaluated at three to six month intervals until the time of death, with sicker participants evaluated more frequently than healthier participants. Assessments include collection of demographic data, standardized medical interview, general physical and comprehensive neurological examination, and assessment of DSM-IV diagnoses of psychiatric and substance use disorders using the Psychiatric Research Interview for Substance and Mental Disorders (PRISM). Laboratory evaluations include CD4+ count, plasma VL, and urine toxicology for substances of abuse (amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, methadone, opiates, phencyclidine, propoxyphene). Data were obtained under a protocol approved by the institutional review board of the Mount Sinai School of Medicine. All research procedures were in accordance with the Helsinki Declaration of 1975, as revised in 2000.

All MHBB participants who were prescribed an opioid, other than methadone, were considered in the analysis. Methadone was excluded because in the vast majority of our participants it is prescribed as methadone maintenance treatment for addiction rather than for pain management. Since data from multiple visits were available for most patients, the first visit at which the opioid appeared on the prescription medication list was used. Problematic opiate use was defined as a positive urine toxicology for substances not

prescribed by a physician (amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, methadone, opiates phencyclidine, propoxyphene), or a current substance abuse or dependence diagnosis for any substance (alcohol, cannabis, cocaine, hallucinogens, opiates, sedatives, stimulants or other substances), as determined by the PRISM. The following potential risk factors for problematic use were available and were considered in the analysis: age, gender, ethnicity, years of education, literacy (as determined by the Wide Range Achievement Test 3 reading subscale; WRAT), past substance abuse or dependence, the presence of any non-substance related psychiatric disorder either current or past (with specific attention to major depressive disorder (MDD), generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD)), CD4+ count, plasma VL, whether ARVs were prescribed, adherence to ARVs, and burden of comorbid illnesses as measured by the Charlson comorbidity index. All psychiatric and substance use diagnoses were determined using the PRISM.

Statistical analyses

We sought to make the best use of the available data and so both cross-sectional and longitudinal analyses were performed, as illustrated in figure 1. In cross-sectional analyses, univariate associations (t-test, Wilcoxon rank sum, or Chi-square as appropriate) were sought between problematic use and: age, gender, ethnicity, years of education, WRAT, CD4+ count, plasma VL, whether ARVs were prescribed, adherence to ARVs, Charlson comorbidity index, PRISM diagnosis of past substance abuse or dependence, any non-substance related psychiatric disorder (current or past considered separately), MDD, GAD, PTSD. Factors associated with problematic use at a significance level of $p < .2$ were considered for inclusion into a multivariate logistic regression model with problematic use as the dependent variable. A backward selection technique was used to find the best model. The subset of participants who did not have problematic use at baseline and had at least one follow-up visit at which they were still prescribed opioids were included in longitudinal analyses. Cox proportional hazards models were used to examine risk factors for future problematic use. We also identified an equal number of contemporaneous participants who were not exposed to prescription opioids, and used similar models to determine if they differed from the opioid prescribed group in rates of future substance misuse. The members of this “unexposed” cohort were chosen to match members of the “exposed” cohort for date of entry into the study and visit number. This was done to allow each group to have similar potential follow-up time. In addition the unexposed group was enriched for participants with a history of substance use in an attempt to have comparable proportions of former substance users in both groups, although individuals were not matched on this basis.

Results

Sample Characteristics

The characteristics of the cross-sectional sample are described in Table 1. Overall the participants were diverse with regard to gender and ethnicity. Most had long-standing HIV and were prescribed ARVs. Substance use history and psychiatric comorbidity were common. Oxycodone and codeine, including combination preparations such as Percocet or Tylenol 3, were the most commonly prescribed opioids.

Cross-sectional univariate analyses

Problematic opioid use was very common in cross-section, 64% of participants met the definition, i.e. they had a positive urine toxicology for a non-prescribed substance or a current PRISM abuse or dependence diagnosis. Among participants with problematic use the most common substance of abuse was cocaine (42%), followed by cannabis (26%), non-prescribed opiates (26%), alcohol (11%), and sedatives (11%). Stimulants and hallucinogens

were used by one patient each. Thirty-four participants (20%) were using more than one substance. Of note there was significance discordance between the results of the urine toxicology and the PRISM. Among the participants with an illicit substance detected by urine toxicology, only 26% reported substance use on the PRISM. This percentage varied by the individual substance (e.g. 37% for cocaine, 19% for cannabis, 10% for non-prescribed opiates) but small numbers and participant overlap between the groups precluded formal comparison.

The results of univariate analyses (t-test, Wilcoxon rank sum, or Chi-square as appropriate) performed to explore associations between problematic opioid use and potential risk factors are shown in table 2. Current non-substance related psychiatric disorder was strongly associated with problematic opioid use ($p=.001$). Among those with a current psychiatric disorder 78% had problematic use compared with 53% among those without a current psychiatric disorder. Three specific diagnoses were investigated: MDD, PTSD and GAD. Problematic use was most closely associated with PTSD ($p=.001$), followed by MDD ($p=.02$) and GAD ($p=.09$). A past substance use diagnosis was also associated with problematic use ($p=.04$). Among past-substance users 67% had problematic use, compared to 46% of those with no past substance diagnosis. Among the participants who were prescribed ARVs, poorer adherence ($<95\%$) was associated with problematic use. Among those with poorer adherence 80% had problematic use, compared to 58% of those who consistently took their ARVs.

Cross-sectional multivariate analyses

Multivariate logistic regression using backward selection was performed with the following variables initially entered into the model: age, past non-substance related psychiatric disorder, current non-substance related psychiatric disorder, past substance use diagnosis, and log (VL). Two variables remained in the model ($p=.001$): current non-substance related psychiatric disorder (OR=3.1; 95% CI 1.5–6.2) and past substance use diagnosis (OR 2.5; 95% CI = .98–6.2).

Adherence was not included in the above analysis because it was not relevant for all patients, since some were not prescribed ARVs. However the same regression as described above with the additional variable of adherence was performed on the subset of participants prescribed ARVs. Two variables remained in the model ($p=.009$): current non-substance related psychiatric disorder (OR=2.5; 95% CI = 1.0–6.0) and poorer adherence (OR 3.55; 95% CI = 1.3–9.5).

Longitudinal analyses

Sixty-two participants did not meet criteria for problematic opioid use in the cross-sectional analysis. Of these, 35 had at least one follow-up visit at which they were still prescribed opioids and were therefore suitable for inclusion in the longitudinal analysis. Among these 35 participants, 10 (29%) had a current non-substance related psychiatric disorder and 28 (80%) had a past substance use diagnosis. The median time of follow-up was 16 months (IQR 10–41). Thirteen (37%) patients displayed problematic use during follow-up. Due to small numbers only the 2 strongest variables from cross-sectional analysis were examined in Cox proportional hazards models: current non-substance related psychiatric diagnosis and past substance use diagnosis. Neither risk factor predicted problematic use ($p>.8$ for both variables).

The characteristics of the prescription opioid exposed and unexposed groups are described in table 3. The groups were similar except the exposed group had a higher burden of comorbid illnesses and a trend for lower literacy. In the unexposed group 10 (29%)

participants had evidence of substance misuse during follow-up. Cox proportional hazards models adjusting for Charlson score and WRAT showed no difference in future substance misuse between the prescription opioid exposed and unexposed ($p = .91$).

Discussion

In this study we sought to explore risk factors for problematic prescription opioid use in a cohort of HIV-infected adults. Our cross-sectional analysis of 173 participants demonstrates an association between problematic use and current psychiatric disorder, past history of substance abuse or dependence, and poor adherence to ARVs. These findings are in keeping with previous literature, most of which was also cross-sectional in design. However an inherent limitation in the interpretation of cross-sectional data is the inability to make inferences about causality. For example, it could be argued that the association of past substance use disorders and problematic use simply demonstrates that those who have abused substances in the past are more likely to be doing so currently and the fact that an opioid has been prescribed is irrelevant and just an artifact of the study design. Another potential limitation of the cross-sectional analysis is its clinical relevance. According to some experts, urine toxicology should be performed before an opioid is prescribed and patients found to be actively using illicit substances should usually not be prescribed opioids. Accordingly longitudinal analyses that were more relevant to the clinical practice recommended by these guidelines were performed. When we followed participants who did not have problematic use at baseline, we found that although a sizable percentage (37%) went on to develop problematic use, past substance use and psychiatric disorder at baseline were not predictive. We also found that participants prescribed opioids were not more likely to develop evidence of a substance use disorder during treatment than participants who were not prescribed an opioid. These findings suggest that although problematic use is associated with active psychiatric illness and past substance use at a given point in time, these factors cannot be used to identify patients who will have problematic use in the future. Furthermore treating these “high-risk” patients with opioids does not appear to increase the rate at which they abuse substances in the future.

How might the discrepancy between cross-sectional and longitudinal data be explained? One explanation is the loss of statistical power from the larger cross-sectional sample to the small longitudinal group. However it is notable that the groups with and without “risk factors” showed very similar cumulative incidence of problematic use (see figure), as demonstrated by the very high p -values ($>.8$). This makes the existence of a true difference less likely even given the very small sample size.

An alternative explanation is that while patients actively abusing substances are likely to have active psychiatric disorders, past substance use disorders and poorer adherence to ARVs, the presence of these factors does not predict future substance misuse in this complicated population. Current guidelines for the general chronic pain population emphasize the importance of risk assessment when considering opioids for treatment of chronic pain.²⁷ Our findings suggest that traditional factors used to assess risk may not be valid in HIV-infected individuals. Thus using these factors when weighing a decision about who to prescribe opioids to might unjustly deprive some patients of a helpful therapy and give the provider a false sense of security when prescribing opioids to other patients. Our findings also have relevance to the use of opioid contracts. We found a significant discordance between patient report of substance use behaviors and the results of urine toxicology, which demonstrates that participants are often not truthful when discussing substance use. This suggests that a patient's agreement to an opioid contract may not be meaningful, especially when they must agree in order to receive opioids.

There are important limitations to this study. Most of the participants have long-standing HIV and/or significant co-morbid illnesses. This may limit generalizability. The data were obtained from an ongoing cohort study not specifically designed for the purpose of this analysis, thus information about problematic behaviors other than illicit substance use, such as diversion, were not available. Similarly we did not have detailed urine toxicology data, capable of distinguishing different opioids, or detailed data about the specific indication for the prescribed opioid. Another limitation is the small number of opioid exposed patients with longitudinal data. However despite these limitations, this study provides important information because it is the first to examine a breadth of risk factors for problematic prescription opioid use in HIV-infected individuals.

In summary our findings demonstrate that problematic prescription opioid use is very common in HIV-infected individuals but cannot be readily predicted based on patient characteristics, and furthermore that self-report of problematic use is not reliable. We do not wish to suggest that opioids are never appropriate for chronic pain in HIV-infected individuals, or that the report of chronic pain should not be taken seriously. Quite the contrary, we have reported previously that in the example of neuropathic pain, self-reported symptoms were highly predictive of an objective neurologic abnormality, namely distal symmetric polyneuropathy.²⁸ However when contemplating opioid treatment for chronic pain in HIV-infected individuals, the provider should be aware that there is a relatively high likelihood that problematic use will develop. Based on the results of this study, we recommend that providers prescribing opioids to HIV-infected individuals avoid opioid contracts and attempts at risk factor assessment and instead adopt “universal precautions” including baseline and follow-up urine toxicologies accompanied by a frank conversation emphasizing that unexpected results will lead to discontinuation of opioid treatment.

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Figure 1. illustrates the selection of participants from the Manhattan HIV Brain Bank cohort for the current study.

Incidence of Problematic Prescription Opiate Use in Participants with and without past substance use disorders

Incidence of Problematic Prescription Opiate Use in Participants with and without psychiatric disorders at baseline

Figure 2. shows no difference in the incidence of problematic prescription opioid use in (a) participants with or without a psychiatric diagnosis at baseline (non-substance related) and (b) participants with or without past substance use.

Table 1Cross-sectional sample characteristics^a

N	173
Age, years	47 (42, 52)
Gender	
Female	43%
Male	57%
Ethnicity	
White	23%
African-American/Black	51%
Hispanic/Latino	24%
Other	1%
HIV duration, years	13 (10, 16.5)
Log (VL, copies/ml)	2.6 (1.7, 4.5)
CD4+ (cells/mm ³)	210 (66, 477)
Prescribed ARVs	80%
95% adherent to ARVs ^b	68%
ARV Class	
NRTI	79%
PI	56%
NNRTI	29%
Entry Inhibitor	3%
Integrase Inhibitor	4%
Current psychiatric disorder ^c	
Any	43%
MDD	30%
PTSD	10%
GAD	3%
Past psychiatric disorder ^c	
Any	67%
MDD	49%
PTSD	24%
GAD	5%
Charlson Score	8 (7, 9)
Past substance use disorder	80%

Years of Education	12 (10, 14)
WRAT	83 (72, 96)
Etiologies of pain	
Neurologic	69%
Musculoskeletal	15%
Cancer	7%
Visceral	4%
Vascular	2%
Unknown	23%
Opioids prescribed	
Codeine	20%
Fentanyl	11%
Hydrocodone	10%
Hydromorphone	5%
Meperidine	1%
Morphine	16%
Oxycodone	50%
Other	2%

Abbreviations: Viral load (VL), antiretroviral (ARV), nucleoside reverse transcriptase inhibitor (NRTI), protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI), major depressive disorder (MDD), post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), wide range achievement test 3 reading subscore (WRAT).

^aValues are median (IQR) unless indicated as a percentage.

^bAmong those prescribed ARVs.

^cExcludes substance induced psychiatric disorders.

Table 2

Cross-sectional analyses of factors associated with problematic prescription opioid use

Factors not significant in univariate association ($p > .2$)	
-Gender	-Literacy (WRAT)
-Ethnicity	-CD4+ count
-HIV duration	-Charlson comorbidity index
-Education	-Prescribed ARVs
Factors marginally significant in univariate analysis ($.05 < p < .2$)	
-Younger age	
-Higher plasma log(VL)	
-Past psychiatric disorder ^a	
Factors significant in univariate analysis ($p < .05$)	
-Current psychiatric disorder ^a	
-Past substance use diagnosis	
-<95% adherent to ARVs	
Factors significant in multivariate analysis ($p = .001$)	
-Current non-substance related psychiatric disorder (OR=3.1; 95% CI 1.5–6.2)	
-Past substance use diagnosis (OR 2.5; 95% CI = .98–6.2).	

Abbreviations: Viral load (VL), antiretroviral (ARV), wide range achievement test 3 reading subscore (WRAT).

^aExcludes substance induced psychiatric disorders.

Table 3Longitudinal cohort characteristics^a

	Exposed to prescription opioids	Unexposed	p-value
N	35	35	
Months of follow-up	16 (10, 41)	18 (9, 40)	.78
Age	50 (41, 53)	49 (45, 53)	.83
Gender			.46
Female	43%	34%	
Male	57%	66%	
Ethnicity			.28
White	34%	34%	
African-American/Black	43%	29%	
Hispanic/Latino	20%	37%	
Other	3%	0%	
HIV Duration, years	13 (10, 16)	13 (10, 17)	.73
Log (VL, copies/ml)	2.03 (1.70, 4.37)	2.00 (1.70, 4.14)	.73
CD4+ (cells/mm ³)	308 (170, 586)	254 (97, 435)	.44
Prescribed ARVs	86%	89%	.72
95% adherent to ARVs ^b	82%	80%	.89
Current psychiatric diagnosis ^c			.61
Any	29%	34%	
MDD	20%	20%	
PTSD	0%	6%	
GAD	0%	3%	
Charlson Score	8 (7, 9)	7 (7, 8)	.007
Past substance use disorder	80%	74%	.57
Years of Education	12 (11, 14)	12 (11, 16)	.60
WRAT	86 (75, 98)	95 (77, 108)	.19

Abbreviations: Viral load (VL), antiretroviral (ARV), major depressive disorder (MDD), post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), wide range achievement test 3 reading subscore (WRAT).

^aValues are median (IQR) unless indicated as a percentage.

^bAmong those prescribed ARVs.

^cExcludes substance induced psychiatric disorders.