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The Role of Key Informants and Direct Patient Interviews in Epidemiological Studies of Substance Abuse

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Abstract

Purpose—The present study was undertaken to assess the degree to which key informants' perceptions of relative abuse liability of opioids in their communities correspond to actual drug use in their patients.

Methods—Key Informants (N=49), and their patients (N=738) were asked to complete anonymous, independent paper surveys about perceived or actual abuse of nine targeted opioid drugs: buprenorphine, fentanyl, heroin, hydrocodone, hydromorphone, methadone, morphine, oxycodone and tramadol.

Results—There was a strong correspondence ($R=.98$) between KI rankings of relative abuse of opioids in their patient population and the actual rank order calculated from their patient's selection of a primary euphorogenic opioid. The patient surveys not only validated the KI's conclusions, but also provided a great deal of important information about the nature of the abuse patterns. Notably, significant co-morbidity was found in the patient population: 55% had a history of psychiatric problems; chronic pain of moderate intensity was common; 67% were nicotine dependent; and 43% were diagnosed alcoholics.

Discussion—Our results demonstrate that KI's perceived rank order of drugs of choice correlated almost perfectly with their patients' choice of a primary drug. These data suggest that key informants, as they have for decades in epidemiological research, provide a reliable, high-level view of substance abuse in their catchment area. As such, KIs provide valid and reliable information on scope and patterns of abuse, but if more detail is required about the characteristics of abuse, such as that required for FDA-mandated Risk Evaluation and Mitigation Strategies (REMS), then direct interviews with the abusers themselves seem more appropriate.

Keywords

post-marketing surveillance; substance abuse; opioids; opioid abuse

Introduction

A new opioid drug entity with suspected abuse liability is nearly always scheduled under the Controlled Substances Act (CSA) I – Schedule II (high abuse potential) > III > IV > V (very low abuse potential). Historically, once this decision is made, there have been no mandated post-marketing studies to measure actual, rather than theoretical, abuse rates. Beginning 15 –

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Conflict of Interest: Dr. Cicero maintains a number of consulting roles with Pharmaceutical firms whose drugs may be included as part of these research activities. Since this is largely a methodological study, it is difficult to envision any actual conflicts of interest.

20 years ago, in the face of massive product recalls including drugs, the Food and Drug Administration (FDA) began to require Phase IV, “post-marketing surveillance” studies⁷ to assess product safety after their release and use by millions of patients. The first program of this type for drugs with abuse potential was the conditional approval of tramadol in 1994². The drug was predicted to have low abuse potential and the Food and Drug Administration (FDA) and sponsor (Ortho-McNeil Pharmaceuticals) mutually agreed that it could be left unscheduled under the CSA, provided an aggressive post-marketing surveillance program was developed to establish whether abuse occurred, estimate its national rates – at a regionally specific level – characterize the abuse and then develop intervention strategies to reduce its incidence if unexpected abuse was found. The effort was overseen by an unprecedented, independent steering committee and has been successful for the last 16 years in meeting the FDA’s requirements, such that tramadol remains unscheduled. This program still exists but has been moved from Ortho-McNeil to the RADARS (Researched Abuse, Diversion and Addiction-Related Surveillance) System^{3, 4}, an independent, not-for-profit operation of Denver Health and Hospital Authority.

The backbone of the tramadol post-marketing surveillance program was the use of a nationwide key informant network. Key informants have played a crucial role for decades in a host of epidemiological and ethnographic studies^{5, 6}. Informants are persons who are well-qualified to provide general information about the incidence or properties of a problem under study. In the case of drug abuse, key informants generally constitute persons knowledgeable about abuse in their community – drug treatment center directors, drug councilors, ethnographers, drug users, drug dealers and others. As such, a network of these informants can provide insights into the “drug scene” in their respective communities. However, given that key informant input is one step removed from the patient or research subject^{7, 8, 9}, it can be argued that these reports represent secondhand interpretations of what the KI *believes* are the characteristics of abuse and abusers and, therefore, may not accurately reflect their patients assessment of drug abuse or the actual drug “scene” in their area. The present study was undertaken to assess the degree to which a key informant’s perception of relative abuse liability corresponds to the reality of abuse patterns in the patients upon whom they have based their conclusions and to discuss the strengths and limitations of both methodologies.

Methods

Data Collection Instruments

Key Informants (N=49), mostly drug treatment center directors, were asked to complete quarterly mail-in questionnaires which queried whether the KI had direct, firsthand knowledge and evidence of dependence on targeted opioid drugs: buprenorphine, fentanyl, heroin, hydrocodone, hydromorphone, methadone, morphine, oxycodone and tramadol. In order to collect demographic details and characteristics of abusers, KI’s were also asked to give an anonymous paper questionnaire to their patients to complete (N=738). These data are collectively referred to as SKIP (Survey of Key Informants’ Patients). They were to recruit as many patients as possible who had a diagnosis of heroin or prescription opioid analgesic abuse or dependence using the DSM-IV. The patient received a packet containing: the questionnaire, a self-addressed stamped return envelope and a \$25.00 gift card. The process was designed to allow the patient to privately complete the survey, place it in the envelope to be mailed without their treatment specialist having access to it, assuring them of complete confidentiality. The questionnaire contained no identifying information insuring complete anonymity. In addition to routine demographic information (age, gender, race, education and employment status), the questionnaire explored sources of prescription drugs, psychiatric co-morbidities, incidence of pain, age at first psychotropic use, drug of choice, and recent use in the past 30 days of both prescription and illicit opioids.

Results

Sample Selection

The distribution of treatment directors (i.e. KIs) and their patients who completed a survey stratified by three-digit postal ZIP codes are shown in Figure 1. As is apparent, there was an excellent geographic distribution of treatment directors and patients: 45% of the samples were in large urban areas (>250,000), with the remainder in small urban (7.8%), or suburban and rural locations (47.2%). Only about one-fourth of those treatment centers that were contacted agreed to participate, while >75% of the patients did so.

Demographics of Key Informants and Misusers

Table 1 shows the demographic and medical histories of SKIP patients; obviously no such data were provided by the KI. As can be seen, drug dependent individuals (N=738) were evenly divided by sex, relatively young, white and with very high rates of recidivism (3 – 4 prior drug treatment events). They also had significant co-morbidity: 55% had a history of serious psychiatric issues (this figure does not include substance abuse); many had chronic pain of moderate intensity; 67% met diagnostic criteria for nicotine dependence; and 43% were diagnosed alcoholics.

Drug Studies

Using DSMIV criteria, we found that 91% of the patients classified by the KIs as being dependent on opioids did, in fact, meet criteria for dependence.

Rank Order

Figure 1B shows the percentage of key informants who indicated that their patients were dependent on the opioids listed on the x-axis contrasted against the percent of patients who ranked these same opioids as their primary drug (i.e. drug of choice). As can be seen, there was a strong correspondence between the two sets of responses with the only significant difference being that KI under-estimated the use of oxycodone and methadone, but the differences overall were quite small. Figure 1C reflects the rank order of abuse of the opioids listed by the KIs and SKIP; there was an excellent correlation ($R=.98$) between the two systems.

Discussion

The use of a key informant network has a long, well-established history in epidemiological and ethnographic studies of abuse^{2, 10} and, as such, KIs were a lynch-pin of the first post-marketing study⁷ mandated by the FDA in 1993 in connection with the approval of Ultram® (tramadol). The data generated by this program were considered so valid and reliable that they were used almost exclusively twice by the FDA's Drug Abuse Advisory Committee and twice by the WHO to better inform decisions on the actual abuse of tramadol and whether any changes in scheduling statutes under the CSA or international drug law were warranted (none were). However successful the tramadol effort any key informant network can be criticized on several levels, the most important of which are that: first, they provide very little detail on the characteristics of abusers which renders detailed research studies into treatment or prevention strategies difficult; and, second, the KI's assessment of abuse rates and drug "popularity" amongst users, is secondhand and could give a false impression of the "drug scene" in their community and, accordingly, direct patient interviews could be more accurate. Regarding the latter point, these concerns seem over-stated and perhaps incorrect.

Our results demonstrate that KI's reports closely match their patients responses in two important respects: first, the KI's assessments that the patients they encountered met criteria

for abuse/dependence seem very accurate given the fact that 90% of their patients satisfied DSMIV criteria for dependence; and, second, the KI's perceived rank order of drugs of choice in their catchment area correlated almost perfectly with their patients choice of a primary drug. As a whole, these data suggest that key informant networks, as they have for decades, provide a reliable, high-level view of substance abuse patterns in geographically-refined areas. However, if more detail is required about the characteristics of users, then key informant networks may not be particularly helpful. Rather, direct interaction with patients would be necessary. Thus, depending on the purpose of the study, key informants can provide valid and reliable information on the scope and patterns of abuse, but if more detail is required then direct interactions with the abusers themselves would be preferred. The recent movement of the FDA towards Risk Evaluation and Mitigation Strategies (REMS) would seem to require more information than that which can be provided by key informants, i.e., detection of a "signal" of abuse. For this reason and our perceived need to better understand the factors driving abuse, the key informant network has been phased out of the original tramadol post-marketing program and the RADARS System in favor of the offshoot program, the survey of the key informants' patients – SKIP.

Our data reinforce the growing body of evidence which indicates that prescription opioid users have a large number of co-morbid physical and psychiatric issues, including chronic pain with moderate intensity, mental health disorders, alcoholism, and nicotine dependence^{11, 12, 13}. As such, substance misuse and abuse certainly do not exist in a vacuum but rather represent one aspect of what appears to be a constellation of co-morbid conditions much like that seen in heroin addicts. Considered in this light, the growth in prescription opioid abuse in the past 10–15 years may represent a different expression of an age-old disease: opioid addiction. What seems to have changed is the selection of the preferred opioid to get high – i.e., prescribed legal drugs rather than heroin.

There are some limitations in the approach we used in this study. Most notably, our sample reflects only those individuals who sought treatment for their abuse problems and, thus, we have very little data on "recreational" users or those who do not opt for treatment. In addition, our survey instruments were self-administered and thus all of the limitations of such methodology need to be recognized. Finally, although we made great efforts to balance the treatment centers – and accordingly our patient interviews – geographically with good representation of urban and rural areas, whether our participants are truly representative of the national population of treatment centers and substance abusers is unknown. Specifically, the KIs and their patients were willing to be interviewed and, at least with respect to the patients, had the resources to pay for treatment. Thus our results may not apply either to all treatment centers or the large body of substance abusers who are not in treatment or who, for whatever reason, choose not to participate in this study. None-the-less it is difficult to imagine that any of these variables would influence our main outcome measure, since our data reflect the correlation between KIs and their patients responses in the same sample no matter how biased it might be.

Take home messages:

- Key informants can provide a meaningful assessment of drug abuse problems in their community.
- Interviews with drug misusers/abusers provide detailed information about abuse characteristics.
- Opioid abusers have significant psychiatric co-morbidity.

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References

1. FDA. Controlled Substances Act. Title 21 - Food and Drugs. Chapter 13 - Drug Abuse Prevention and Control. Subchapter I - Control and Enforcement. [accessed 29 April 2010]. <http://www.fda.gov/RegulatoryInformation/Legislation/ucm148726.htm>
2. Cicero TJ, Adams EH, Geller A, Inciardi JA, Munoz A, Schnoll SH, Senay EC, Woody GE. A postmarketing surveillance program to monitor Ultram® (tramadol hydrochloride) abuse in the United States. *Drug Alcohol Depend.* 1999 Nov 1; 57(1):7–22. [PubMed: 10617309]
3. Cicero TJ, Inciardi JA, Munoz A. Trends in abuse of OxyContin and other opioid analgesics in the United States: 2002 – 2004. *J Pain.* 2005 Oct; 6(10):662–672. [PubMed: 16202959]
4. Dart RC. Monitoring risk: post marketing surveillance and signal detection. *Drug Alcohol Depend.* 2009 Dec 1; 105 Suppl 1:S26–S32. Epub 2009 Sep 12. [PubMed: 19748743]
5. Needle R, Kroeger K, Belani H, Achrekar A, Parry CD, Dewing S. Sex, drugs, and HIV: rapid assessment of HIV risk behaviors among street-based drug using sex workers in Durban, South Africa. *Soc Sci Med.* 2008 Nov; 67(9):1447–1455. Epub 2008 Aug 3. [PubMed: 18678437]
6. Ferrer RR, Balasuriya D, Iverson E, Upperman JS. Pediatric disaster preparedness of a hospital network in a large metropolitan region. *Am J Disaster Med.* 2010 Jan–Feb; 5(1):27–34. [PubMed: 20349700]
7. Butler SF, Budman SH, Licari A, Cassidy TA, Liroy K, Dickinson J, Brownstein JS, Benneyan JC, Green TC, Katz N. National addictions vigilance intervention and prevention program (NAVIPPRO): a real time, product-specific, public health surveillance system for monitoring prescription drug abuse. *Pharmacoepidemiol Drug Saf.* 2008 Dec; 17(12):1142–1154. [PubMed: 18932173]
8. Katz NP, Adams EH, Benneyan JC, Birnbaum HG, Budman SH, Buzzeo RW, Carr DB, Cicero TJ, Gourlay D, Inciardi JA, Joranson DE, Kesslick J, Lande SD. Foundations of Opioid Risk Management. *Clin J Pain.* 2007 Feb; 23(2):103–118. [PubMed: 17237659]
9. Katz N, Panas L, Kim M, Audet AD, Bilansky A, Eadie J, Kreiner P, Paillard FC, Thomas C, Carrow G. Usefulness of prescription monitoring programs for surveillance--analysis of Schedule II opioid prescription data in Massachusetts, 1996–2006. *Pharmacoepidemiol Drug Saf.* 2010 Feb; 19(2):115–123. [PubMed: 20014166]
10. Cicero TJ, Dart RC, Inciardi JA, Woody GE, Schnoll S, Muñoz A. The Development of a Comprehensive Risk-Management Program for Prescription Opioid Analgesics: Researched Abuse, Diversion and Addiction Related Surveillance (RADARS®). *Pain Med.* 2007 Mar; 8(2):157–170. [PubMed: 17305687]
11. Catalano J. Pain management and substance abuse: a national dilemma. *Soc Work Public Health.* 2009 Nov–Dec; 24(6):477–490. [PubMed: 19821188]
12. Gilson AM, Kreis PG. The burden of the nonmedical use of prescription opioid analgesics. *Pain Med.* 2009 Jul. 10 Suppl 2:S89–S100. [PubMed: 19691688]
13. Cicero TJ, Lynskey M, Todorov A, Inciardi JA, Surratt HL. Co-morbid pain and psychopathology in males and females admitted to treatment for opioid analgesic abuse. *Pain.* 2008 Sep 30; 139(1):127–135. Epub 2008 May 1. [PubMed: 18455314]
14. FDA. Guidance for Industry - Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications. [accessed 29 April 2010]. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>

Figure 1.

A shows the location – stratified by 3 digit ZIP code of all Key Informants and their patients who completed a questionnaire.

B Percent of Key Informants indicating they had evidence of individuals dependent on the drugs listed on the x-axis contrasted to the percent of their patients who selected these same opioids as their primary drug.

C shows the rank order of the prevalence of opioid misuse cases reported by the KIs and their patients (SKIP). 1 = most frequently misused; 9 = least frequently misused.

Table 1

Characteristics of Prescription Opioid Abusers

		N = 738
Gender	<i>Female</i>	51.04%
	<i>Male</i>	48.96%
Average Age		35.8 ± 0.42
Ethnicity	<i>White</i>	84.68%
	<i>African-American</i>	4.92%
	<i>Latino/a</i>	4.38%
	<i>Other race</i>	6.02%
Met DSM-IV criteria for abuse		90.75%
Average number of times prior treatment sought		3.9 ± 0.35
Average Chronic Pain Score		5.0 ± 0.11
Ever Treated for Psychiatric Disorder (other than substance abuse)		55.28%
Met criteria for Nicotine dependence		66.80%
Met criteria for Alcohol abuse		42.68%