



Does multisite sampling improve patient heterogeneity in drug misuse research?

John Dunn ^{a,*}, Cleusa Pinheiro Ferri ^b, Ronaldo Laranjeira ^b

^a Academic Department of Psychiatry, Royal Free and University College Medical School, Royal Free Hospital, Pond Street, London, NW3 2QG, UK

^b UNIAD (Unidade de Pesquisa em Alcool e Drogas), Departamento de Psiquiatria, Escola Paulista de Medicina, Universidade Federal de São Paulo, Rua Botucatu, 740, São Paulo-SP, 04023-900, Brazil

Received 14 January 2000; received in revised form 16 May 2000; accepted 1 August 2000

Abstract

The aim of this study was to investigate whether multisite sampling increased heterogeneity among a sample of cocaine users from São Paulo, Brazil. Six hundred and fourteen cocaine users were interviewed at 23 fixed sites plus an out-of-treatment sample. The sites were then regrouped into six main types: university outpatient clinics, public outpatient clinics, public inpatient units, private inpatient units, HIV services and non-treatment. Marked differences were found between users recruited at these sites, especially in relation to age, gender, employment status, criminal history, history of prostitution, previous drug misuse treatment, duration of cocaine use and lifetime use of intravenous cocaine. These results suggest that multisite sampling is a valid method for increasing patient heterogeneity, but whether it improves representativeness and thus the generalisability of drug misuse research is debatable. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Substance misuse; Cocaine; Epidemiological methods; Sampling; Brazil

1. Introduction

Probability sampling is the gold standard for obtaining representative samples of individuals from a population. However, when drug misusers are the target group various problems arise which mean that probability sampling can become impracticable (Dunn and Ferri, 1999). First, there is the problem of low prevalence. For example, an estimate from the UK suggests that around 2% of the general population are dependent on illicit drugs (Farrell et al., 1998). However, it is likely that less than a quarter of these are dependent on individual substances, such as cocaine. Consequently, to find just one cocaine addict, one might need to interview at least 400 people. To find enough cocaine addicts (300 for example) to allow us to make statistically powerful statements

about their characteristics, we might need to interview over 120 000 people. The larger the sample, the longer it will take to complete the interviews, the more expensive the study becomes and since the ratio of cases to non-case is very low, the more inefficient the whole process becomes.

A second problem with probability sampling is that illegal activities, such as drug misuse, may be hidden or denied, so it can be difficult to find or identify users. Surveys tend to be based on the occupants of private households, so cocaine addicts may be missed because they are out buying drugs or involved in illegal activities to finance their use or because they are homeless, in prison or in residential treatment (Dunn and Ferri, 1999). Consequently many research studies that aim to investigate the characteristics of drug users and their patterns of use tend to employ convenience samples using patients from outpatient and inpatient units (Griffin et al., 1989; Kleinman et al., 1990; Dunn et al., 1996). However, selection bias means that drug users recruited from these settings have very different characteristics to those who are

* Corresponding author. Tel.: +44-20-77940500, ext. 3719/3950; fax: +44-171-8302808.

E-mail address: drjdunn@hotmail.com (J. Dunn).

not in treatment. Studies suggest that drug users not in treatment are more likely to be polydrug users, be involved in illegal activities but have fewer negative consequences of drug use and less depression (Rounsaville and Kleber, 1985; Carrol and Rounsaville, 1992).

If only one treatment service were used for sampling then the patients accrued might be very homogeneous due to factors such as geographic location, public or private status, type of treatment offered and admission criteria. In recent years attempts have been made to recruit more patients from non-treatment settings using snowball sampling (Lopes et al., 1996), privileged access interviewer techniques (Griffiths et al., 1993) or by directly approaching suspected drug users on the streets (Edlin et al., 1994), but none of these methods is immune from selection bias. Patients nominating drug-using friends or colleagues who are not in treatment, may be more likely to indicate people who share similar sociodemographic and drug use characteristics as themselves.

Multisite sampling has been offered as a way of increasing patient heterogeneity and representativeness (Haw et al., 1992). With this method, although sampling bias may still operate at each site, it is postulated that with a large enough number of sites, these biases will tend to cancel each other out. However, we cannot assume that this will happen, if the biases are mainly acting in the same direction, then the final sample may not be as heterogeneous or representative as was hoped. Multisite sampling is widely used in research studies of drug misuse and HIV (Lewis et al. 1992; Gossop et al., 1998; Deren et al., 1998) but is it valid? The aim of this study was to investigate whether multisite sampling increased heterogeneity among a sample of cocaine users.

2. Methods

The sample used in this analysis was combined from two separate studies that had been undertaken concurrently. The first sample (study I) was from Dunn and Laranjeira's study of the profiles, patterns of drug use and HIV-risk behaviours among cocaine users in Sao Paulo (Dunn and Laranjeira, 1999a). The second sample (study II) came from Ferri and Gossop's study comparing treatment seeking and out-of-treatment cocaine users, also in Sao Paulo (Ferri and Gossop, 1999). Although each study had different objectives, their questionnaires had many identical items, in particular those concerning demographic details and drug misuse history. More detailed information about the methodology used in each study can be obtained from previously published work, in particular Dunn and Laranjeira (1999b) and Ferri and Gossop (1999).

2.1. Setting

This was a cross sectional study with drug users interviewed between January 1996 and December 1997. In total 23 different treatment and counselling services were used in addition to an out-of-treatment sample. The characteristics of each site are summarised in Table 1. All services are situated in the State of Sao Paulo and most are from the City of Sao Paulo itself.

2.2. Sampling

Three main sampling techniques were used: systematic sampling in the treatment services and a combination of snowball sampling and privileged access interviewer technique for the non-treatment sample. At the treatment sites an attempt was made to interview all available patients, but due to time constraints this was not always possible. In this situation patients were interviewed according to the order in which their names appeared on the inpatient lists or in order of arrival at the outpatient clinics. Data were not collected on patients who were not interviewed. A snowball sample of 68 cocaine users was obtained by asking users in treatment settings to nominate a cocaine using friend or colleague who was not currently in treatment. A further 27 out-of-treatment cocaine users were contacted mainly through non-drug users who knew people who used cocaine within their own social or professional network, including a dentist, a porter and several drugs workers.

2.3. Procedures

In study I 294 patients were interviewed by a team of three researchers using a questionnaire that had been developed and piloted in Brazil. In study II 332 patients were interviewed by a team of ten researchers using a questionnaire that had been translated from English. In both studies patients gave verbal consent and were guaranteed confidentiality as well as anonymity due to the very private and often illegal nature of the activities they were being asked about. Both projects were approved by the Ethics Committee.

Of the 23 sites included in the study three were visited by both research teams, although rarely at the same time. Checks were made to see if duplicate cases had been included by comparing the dates of birth of patients interviewed at these sites. Patients with identical birthdays had their questionnaires compared to see if their main demographic details were also identical (sex, level of schooling, marital status and profession). Three duplicate cases were found and excluded.

Compared to study I, study II had the stricter entry criteria: use of cocaine at least twice per week for three months versus lifetime use of cocaine on more than one

occasion. When the stricter criteria were applied to the study I sample, nine patients had to be excluded as they had never used cocaine with such a high frequency. The final sample size after exclusions was 614.

2.4. Statistics

For statistical purposes sites that shared common characteristics were grouped together into the following categories: public teaching hospital outpatient clinics ($n = 3$), other public outpatient/counselling services ($n = 5$), public hospital inpatient units ($n = 2$), HIV treatment services and hospices ($n = 8$), private inpatient units ($n = 5$) and an out-of-treatment sample. The two continuous variables that were investigated (age and duration of cocaine use) were skewed to the right and underwent transformation. A logarithmic transformation was used for age (transformed mean = 3.25, S.D. = 0.28, range 2.37–4.04) and a square-root transformation for duration of cocaine use (transformed mean = 2.59, S.D. = 0.99, range 0.40–6.16). All comparisons are between the

six grouped sites. Age and duration of cocaine use were analysed using one-way analysis of variance. Gender differences were investigated using the X^2 test. Because there were substantial differences between sites in relation to age and duration of cocaine use, all other binary variables were analysed using logistic regression analysis so that the effects of these variables could be controlled for. In general, demographic variables were controlled for the effects of age, whilst drug and crime related variables were controlled for the effects of duration of cocaine use. Since all the statistical tests undertaken in this study were conceptually linked, a Bonferroni correction was made. Sixteen statistical tests were performed and the adjusted significance level was $P = 0.0031$. Some variables were not tested because the vast majority of subjects shared that characteristic. This was true for lifetime use of the following substances: cannabis (96%), snorted cocaine (96%), alcohol (91%) and cigarettes (86%). As frequent cocaine use was used as a criterion for entry into the study, this variable was not submitted to statistical analysis.

Table 1
Characteristics of the 24 individual sites that were used in this study

Site name	Type of service	Status	Clientele	Number interviewed
UNIAD	Outpatients	Public	Drugs and alcohol	131
PROAD		Teaching		17
Santa Casa		Hospitals		1
PROSAM	Outpatient	NGO ^a	Drugs	30
DENARC	Counselling	Police	Drugs	40
NAT	Outpatients	Public	Drugs and alcohol	6
PAM		Municipal		14
CRTF		Clinics		15
Agua Funda	Inpatient units	Public	Drugs and alcohol	64
Taipas				73
CRAIDS	Outpatient HIV services	Public clinics	HIV/AIDS	33
DIPA				9
Taipas-HIV				1
Brenda Lee	Hospices and nursing homes for people with HIV	NGOs or Charitable	HIV positive	6
Lar Betânia			drug users, prostitutes,	6
Associação Paz			transvestites and	2
Projeto Esperança			transsexuals	2
Associação Lar				10
Instituto Bairral	Inpatient units	Private	Drugs and alcohol	15
Greenwood				7
Vila Serena				8
Nossa Senhora			General	11
João de Deus			psychiatric	19
Non-treatment	Snowball PAI ^b	—	Regular cocaine users	68 27

^a Non-governmental organisation.

^b Privileged access interviewer technique.

3. Results

Six hundred and fourteen cocaine users were eligible for inclusion in the analysis. The differences between users in relation to the sites at which they were interviewed are shown in Table 2. In terms of demographic characteristics, age and sex are the most strikingly different between sites. Cocaine users in the HIV treatment services were on average 8 years older than those in the public outpatient clinics. Previous episodes of drug misuse treatment were very infrequent in the HIV services and not surprisingly in the out-of-treatment sample, whilst two-thirds of those interviewed in inpatient units had had prior treatment. Prostitution, or rather exchanging sex for drugs or money to buy drugs, showed a 6-fold variation between sites being highest among those in HIV treatment centres. Criminal activity was also highest among patients seen in HIV services as well as those in public inpatient units. However, drug dealing was equally common among cocaine users from each principal site. In terms of cocaine history, patients seen in HIV services had the highest frequency of lifetime injecting of cocaine. Duration of cocaine use varied substantially between sites with those in HIV services having used for twice as long as those in public outpatient units.

These differences between sites led us to ask how much individual sites were contributing to the overall heterogeneity and whether certain sites were sampling distinct patient populations? To look at this question we ranked each of the 16 variables studied from 1 to 6 (these values representing the rank order of each of the six sites). As each variable has a maximum and minimum value, there should be 32 extreme values representing these upper and lower limits. However, as three upper values were tied (the proportion who had committed armed robbery), there were in fact 34. Ten of these extreme values came from the HIV services sample. The results show that this group tended to be older, married, unemployed, more likely to have been arrested, to have prostituted themselves, to have had little previous drug treatment, to have a higher probability of having used amphetamines, tranquillisers and of having injected cocaine and to have been using cocaine for longer. Eight extreme values in the opposite direction were found for the public hospital outpatient sample. These patients tended to be younger, single, poorly educated, less likely to have been arrested and involved in drug dealing, unlikely to have used amphetamines or to have injected cocaine and to have been using cocaine for less time. However, some extreme values were found for each of the remaining four sites, ranging from three for the university outpatient sample to five for the private inpatient group.

When the upper and lower limits of each variable were examined in relation to the pairs of sites in which

they occurred, six pairings were found to occur between the HIV and public outpatient samples. The remaining ten pairings each occurred in a separate sample permutations with no further repetitions. Calculating the mean rank difference between pairs of sites for the 16 variables studied, showed that the two sites closest in terms of patient characteristics were the university outpatient and the public hospital outpatient samples (mean rank difference = 1.6, range 1–4 — from a possible range of 0–5). However, even though these two sites were relatively similar, there were still some statistically significant differences between them. Differences were found in relation to mean age ($t = 3.33$, d.f. = 252, $P = 0.001$) and level of schooling ($X^2 = 13.7$, d.f. = 2, $P = 0.001$) and differences bordering on the statistically significant ($P = 0.06$) for lifetime use of amphetamines and duration of cocaine use.

4. Discussion

This study shows that cocaine users interviewed at diverse sites had markedly different characteristics, in terms of demographic features, criminal history, history of prostitution, previous drug treatment and drug use history. This suggests that by increasing the number of sites used for patient recruitment, and by including non-treatment settings, we can obtain more heterogeneous samples of drug users.

In a study similar to ours, Lewis et al. (1992) interviewed 1003 crack abusers from six types of locale in New York City: streets where drug users do their business, jails, probation parole services, prisons, drug abuse treatment settings and courts. In the analysis the authors focus on differences in demographic features, including sex, age, race, education, marital status and employment, but not on patterns of drug use. The sampling strategy used in their study differed from ours in that predetermined quota targets were used to make sure that certain subgroups were not under sampled, in particular females and adolescents. Consequently, it is difficult to compare results. However, variation between locales was found, especially in relation to race and employment status. In the United Kingdom National Treatment Outcome Research Study (Gossop et al., 1998), 1075 drug users undergoing treatment at 54 agencies were compared in terms of treatment modality: inpatient, residential rehabilitation, methadone maintenance and methadone reduction. Substantial differences were found between groups, especially in relation to age, duration of heroin use, criminal history, treatment history and drug use history. As this was a treatment outcome study, there were no out-of-treatment subjects.

Some potential sites where large numbers of drug users might have been found, such as prisons and illicit drug markets (Lewis et al., 1992), were not included in

Table 2
Differences between cocaine users interviewed at six grouped sites in relation to demographic characteristics and drug use history ($n = 614$)

Variable	University outpatient ($n = 149$, %)	Public outpatient ($n = 105$, %)	Public inpatient ($n = 137$, %)	HIV service ($n = 68$, %)	Private inpatient ($n = 60$, %)	Non-treatment ($n = 95$, %)	<i>P</i> value ^a
Age (years), mean (S.D.) ^b	26.4 (7.57)	23.5 (7.29)	26.4 (6.96)	31.4 (6.42)	29.1 (9.32)	26.8 (7.58)	$P < 0.0001^c$
Sex (male)	96	93	92	79	76	88	$P < 0.0001^c$
<i>Marital status:</i>							
Single	65	76	57	46	58	75	$P = 0.058$
Married/other	36	24	43	54	42	27	
<i>Schooling:</i>							$P = 0.019$
Primary	61	80	70	69	58	77	
Secondary or above	39	20	30	31	41	23	
Employed	40	34	34	19	43	30	$P = 0.003^c$
<i>Crime:</i>							
Theft	38	52	61	60	45	58	$P = 0.0006^c$
Armed robbery	15	18	32	32	10	32	$P < 0.0001^c$
Drug dealing	30	29	33	37	32	40	$P = 0.475$
Arrested	48	39	56	85	46	48	$P < 0.0001^c$
Prostitution	4	6	14	25	20	24	$P < 0.0001^c$
Past treatment	46	42	65	24	63	20	$P < 0.0001^c$
<i>Lifetime use of:</i>							
Amphetamine	19	10	19	38	30	11	$P = 0.009$
Tranquillisers	38	35	51	56	38	24	$P = 0.0007^c$
I.V. cocaine	17	13	20	78	28	27	$P < 0.0001^c$
Crack	85	83	92	76	75	82	$P = 0.053$
Duration of cocaine use, years (S.D.) ^b	7.1 (5.18)	6.1 (5.20)	7.5 (5.60)	11.0 (5.50)	9.5 (7.80)	7.7 (4.79)	$P < 0.0001^c$

^a All analyses were corrected for the effects of age or duration of cocaine use, except age and duration themselves and sex.

^b Age underwent a natural logarithmic transformation and duration of cocaine use a square-root transformation prior to analysis.

^c With Bonferroni adjustment, significance level is $P = 0.0031$.

our study. A decision was taken during the planning stage not to interview drug users at these sites, due to a lack of safety (staff and visitors had been kidnapped and seriously assaulted by prisoners at the time of the study). Furthermore, there may have been an over representation of cocaine users from treatment sites, in particular public treatment agencies. One might predict that this would tend to reduce heterogeneity and amplify the differences between treatment and non-treatment samples. However, this does not appear to have been the case, indeed the greatest absolute differences between variables occurred between treatment agencies.

An important question is how necessary was it to have interviewed patients from all six sites? Two sites in particular (HIV services and public hospital inpatient services) were responsible for many of the more extreme values in both directions and appear to be sampling quite distinct patient subgroups. However, each of the other four sites was responsible for at least three extreme values. Even between the two sites that were most similar (university hospital outpatient clinics and public hospital outpatient/counselling services), some statistically significant and clinically important differences were found. Therefore, it is clear that each site contributed to the overall heterogeneity, although to differing degrees.

Our findings confirm that some treatment services attract patients with markedly different characteristics. One implication of this finding is that if multisite sampling were used as a proxy for probability sampling, to estimate the prevalence of a particular behaviour, then the result would be greatly influenced by the choice of sites. Over representation of sites with similar characteristics would affect the estimate. For example, the prevalence of reported prostitution varied from 4% among cocaine users treated at university hospital outpatient clinics to 25% among those seen at specialist HIV services. Therefore, if probability sampling is impracticable, we must ensure that drug users from a wide range of treatment agencies and out-of-treatment locations are used, otherwise our estimates may be wide of the mark.

In other research designs, such as cohort studies or case-control studies, the differential prevalence of potential risk factors between sites will not affect the conclusions that these studies reach but it will affect any power calculations that are performed beforehand. If, for example, one were to look at a history of prostitution as a risk factor for HIV seroconversion, then it would make a huge difference to the number of patients one would need to interview to show a statistically powerful association if the prevalence of the behaviour were 4 or 24%.

In cross-sectional studies looking at the association between variables, for example the relationship between severity of dependence and HIV-risk behaviour

(Gossop et al., 1993), the more heterogeneous the sample in relation to these variables the better. If one only interviewed patients who scored very high on a measure of dependence, then there may be insufficient variability to be able to show an association. Correlations can best be demonstrated when the variables being studied exhibit a wide spread of values rather than being clustered around the upper limit.

Although multisite sampling appears to increase patient heterogeneity, we cannot be certain that it makes samples more representative. The relationship between heterogeneity and representativeness is unclear. Because selection bias operates in different ways at different sites, we may have inadvertently over or under sampled certain subgroups of cocaine users, such as men and younger cocaine users. This could have affected the overall representativeness of the sample. The only way we could have avoided this is if we had used quota sampling developed from a knowledge of the characteristics of the sampling frame, i.e. all cocaine users in São Paulo. However, this information is rarely available and in Brazil is certainly not available.

This study shows that multisite sampling is a valid procedure for increasing patient heterogeneity, but without information on the sampling frame it cannot be shown to improve representativeness. Since representativeness is the key to generalisability, this is a serious limitation. The relative importance of heterogeneity or representativeness will depend on the hypothesis being tested and the study design.

Acknowledgements

Dr J. Dunn received a fellowship from the Brazilian Research Council (CNPq) and his work was in part funded by a grant from FAPESP. Dr C.P. Ferri received a fellowship from CAPES and part of her work was also funded by FAPESP. We gratefully acknowledge the statistical advice from Bob Blizzard, statistician, Academic Department of Psychiatry, Royal Free Hospital.

References

- Carroll, K.M., Rounsaville, B.J., 1992. Contrast of treatment-seeking and untreated cocaine abusers. *Arch. Gen. Psychiatry* 49, 464–471.
- Deren, S., Beardsley, M., Coyle, S., Singer, M., 1998. HIV serostatus and risk behaviors in a multisite sample of drug users. *J. Psychoactive Drugs* 30, 239–245.
- Dunn, J., Ferri, C.P., 1999. Epidemiological methods for research with drug misusers: review of methods for studying prevalence and morbidity. *Rev. Saude Publica* 33, 206–215.
- Dunn, J., Laranjeira, R.R., Silveira, D.X., Formigoni, M.L.O., Ferri, C.P., 1996. Crack cocaine: an increase in use among patients attending clinics in São Paulo 1990–1993. *Subst. Use Misuse* 31, 519–527.