Do Young Heroin Users in Madrid, Barcelona and Seville have Sufficient Knowledge of the Risk Factors for Unintentional Opioid Overdose?

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ABSTRACT *To identify the self-perceived reasons for unintentional opioid overdose of young heroin users in three Spanish cities and their agreement with objective risk factors for overdose. Computer-Assisted Personal Interviews (CAPI) were held with 991 street-recruited current heroin users aged 18–30. The general reasons for overdose and the reasons for the last overdose suffered were explored with open-ended (OEQs) and pre-coded questions (PCQs). Limited knowledge of overdose risk factors was defined as mention of fewer than two objective risk factors for unintentional overdose in the OEQ. Univariate, bivariate, and logistic regression methods were used. 77.8% (Seville), 64.9% (Madrid) and 57.2% (Barcelona) of participants have limited knowledge of overdose risk factors. Residence in Seville and not having attended courses or meetings on overdoses were significantly associated with limited knowledge, after adjusting for other factors. The most frequently identified general reasons in OEQ or PCQ were using heroin in large amounts (66.8%), together with tranquilizers (62.0%), adulterated (60.7%), or purer than usual (57.6%). Most reasons were selected more frequently in PCQ than in OEQ, especially rapid injection of the entire dose and using heroin shortly after using tranquilizers or alcohol, by injection, or after a period of abstinence. The results were similar for overdoses suffered by participants. Most young heroin users do not have sufficient knowledge of overdose risk factors, especially the use of heroin by injection, after a period of abstinence, or together with alcohol or methadone. Specific informational or educational programs adapted to the local context are critically needed.*

KEYWORDS *Heroin, Opioid overdose, Self-perceived reasons.*

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INTRODUCTION

Acute opioid overdose is frequent among heroin users (annual prevalence of 9–33%) and is an important cause of death and emergency care.^{1–5} Based on published data,^{6,7} it can be estimated that overdoses have caused more than 20,000 deaths in Spain in the last 25 years. In 2000, acute overdose from illegal drugs (in over 85% of which opioids were detected) caused 4% of all deaths in Spain in persons aged 15–49, with rates of 13.8/100,000, 7.0/100,000, and 7.4/100,000 for the cities of Barcelona, Madrid and Seville, respectively.^{7–9} Furthermore, in 1999 overdose was again the leading cause of death among heroin users in Barcelona, surpassing HIV infection.¹⁰

The main objective risk factors for opioid overdose detected in epidemiological studies of association are injecting heroin, using opioids together with benzodiazepines or alcohol, not being in methadone treatment, and using opioids after a period of abstinence, generally due to having been in prison or drug-dependency treatment. Risk factors that have been cited less frequently are the use of very pure or a large amount of heroin, the presence of some health problems, the use of heroin together with cocaine, the use of methadone alone or together with benzodiazepines or alcohol, and attempted suicide.^{4,10–21} A comparison of these objective risk factors with the reasons for overdose self-perceived by users, a subject addressed by few studies to date,^{2,22–24} could provide some guidance on the need for specific programs to prevent overdoses or for a change in our approach to these programs.

The objective of this study is to examine the reasons for opioid overdose self-perceived by heroin users in three Spanish cities (Madrid, Barcelona and Seville) and how well these agree with objective risk factors for overdose. There are important differences in the mortality rate from overdose in these cities, as previously indicated, as well as in their patterns of heroin use. For example, they represent three very different epidemiological profiles with respect to the main route of heroin administration: in Barcelona, the intravenous route predominates; in Madrid, smoking has been the most frequently employed route since the mid nineties; and in Seville, smoking has predominated since the end of the eighties.^{25,26} It is also likely that general harm-reduction programs, as well as specific programs to prevent overdose, have been developed differently in these cities, making it possible to analyze the relevance of the cultural and social context in users' knowledge and opinions.

MATERIALS AND METHODS

The methodology used in this study has been described in detail elsewhere.²⁶

Subjects

Between April 2001 and December 2003 we recruited 991 heroin users for the *Itínere* cohort. All subjects were between 18 and 30 years of age, had used heroin at least 12 days in the 12 months before the baseline visit and at least one day in the three previous months, and resided in the metropolitan areas of Madrid, Barcelona or Seville. The entire sample was street recruited by chain-referral procedures (targeted sampling and respondent-driven sampling—RDS),²⁷ regardless of whether or not they were in treatment. Recruitment from treatment or health centers was

avoided. Research workers visited all the important targets (drug scenes), mainly areas of drug sales or major drug use, to recruit the initial participants (17.1%); 1.7% of participants responded directly to recruitment announcements, 34.1% were enrolled by key informants, and 47% were enrolled by participants themselves using RDS. We attempted to keep direct recruitment of participants in the first wave proportional to the assumed size of each target. Incentives for being interviewed and for recruiting other participants into the study were offered (18€).

Data Collection

A questionnaire was administered by Computer-Assisted Personal Interview (CAPI),^{28,29} programmed using the *Questionnaire Development System (QDS)* software.³⁰ Information was included on sociodemographic variables, patterns of drug use, perceived dependence, sexual and injection behavior, perceived health, mental health, use of social and health services, and non-fatal opioid overdoses. To construct the section on non-fatal opioid overdoses, in-depth interviews were held with 20 heroin users. Overdose was defined as an episode occurring after heroin or opioid use characterized by extreme difficulty in breathing, loss of consciousness and problems waking up or recovering consciousness, and possibly bluish skin or lips. We first investigated the self-perceived reasons for overdose in general. To do this, all participants were asked in an open-ended question (OEQ) to list all the reasons for overdose they could think of and then to select three reasons in order of importance from a closed list of pre-coded questions (PCQ). We then investigated the reasons for overdoses experienced by asking those who had suffered an overdose to explain in an OEQ all the reasons for the last such episode, including the most important one. By using OEQs, it is possible to determine the importance that users spontaneously give to different reasons for overdose, some of which might not have been considered in the PCQ. This approximation to the free-listing technique,³¹ as a way to explore the free and spontaneous discourse of the person interviewed, was carried out before presenting the PCQ, to avoid suggesting any particular reason to the study subjects.

Data Analysis

The reasons cited in each OEQ were transcribed verbatim. Before coding the reasons, two investigators, A and B, independently grouped those with a similar underlying concept and created two detailed lists of categories. The differences were then discussed, and a single list was agreed on. The coding was done by two new investigators, C and D, who independently classified each reason in one category of the list, and the discrepancies (15.9–18% of the replies) were resolved by investigators A and B. Some of the reasons cited included two or more concepts; therefore, they were classified in two or more categories. The proportion of participants who cited each category was calculated in relation to all those who answered the question. Some persons cited reasons that were inappropriate, meaningless or could not be classified (1.7–2.8%). About 7.2% (overdose in general) and 7.5% (overdose suffered) of subjects did not cite any reason. The proportion of non-responses in the PCQ was 2.9%. To make the list easier to read, the detailed reasons were grouped into larger categories (groups of reasons). A participant was considered to have “limited knowledge” of the risk factors for unintentional overdose if, in the OEQ, the person cited fewer than two of the following nine overdose risk factors: using heroin in a large amount, purer than usual, together with tranquilizers, with alcohol, with cocaine, by the intravenous

TABLE 1. General characteristics of young heroin users recruited in Barcelona, Madrid and Seville, 2001–2003 (%)

	Barcelona	Madrid	Seville	Total	
	(<i>n</i> = 364)	(<i>n</i> = 427)	(<i>n</i> = 200)	(<i>n</i> = 991)	
Males	69.0	71.7	82.5	72.9	**
25 years or less	53.3	32.8	41.5	42.1	***
Primary or lower educational level	34.1	41.1	76.5	45.7	***
Unemployed most of the time ^a	56.8	54.6	56.1	56.1	ns
Most income obtained by stealing, selling drugs and marginal activities ^a	30.5	32.6	33.0	31.9	**
Homeless or without fixed residence most of the time ^a	43.7	14.1	17.0	25.5	***
Any prison stay ^a	11.8	8.7	5.0	9.1	*
Drug use 5 years or less	37.4	22.7	25.5	28.7	***
Current main route of heroin administration ^a					***
Smoked	28.3	82.9	99.0	66.1	
Injected	59.3	16.9	1.0	29.3	
Sniffed in powdered form	12.4	0.2	0.0	4.6	
Frequency of heroin use ^a					***
More than 4 days/week	47.8	58.3	69.0	56.3	
1–4 days/week	37.9	31.6	24.0	32.4	
Less than weekly	15.1	10.1	7.0	11.3	
Frequency of tranquilizer use ^a					***
More than 4 days/week	30.3	32.4	20.0	29.1	
1–4 days/week	25.9	23.5	25.0	24.7	
Less than weekly	28.4	30.5	21.0	27.8	
Not used	15.4	13.6	34.0	18.4	
Daily tobacco consumption ^a	97.0	95.6	95.5	96.1	ns
Daily consumption of 50 ml or more of pure alcohol ^a	30.6	33.9	36.7	33.3	ns
Prevalence of other drug use ^a					
Cocaine base	62.0	89.7	85.0	78.6	***
Powdered cocaine	89.0	69.1	62.0	75.0	***
Ketamine	34.9	4.2	3.0	15.2	***
Ecstasy	50.8	26.5	18.0	33.8	***
Amphetamines	44.1	16.6	11.0	25.6	***
Tranquilizers or sleeping pills	84.3	86.4	66.0	81.5	***
“Street methadone” ^b	32.0	29.7	57.0	36.1	***
Opioids other than heroin or methadone	54.4	42.2	12.0	40.6	***
Cannabis	93.1	85.7	87.0	88.7	**
LSD	27.8	10.1	10.5	16.7	***
Inhalation of volatile substances	10.7	6.6	4.5	7.7	*
Drug injection ^a					***
No	24.6	52.7	86.2	49.1	
Yes, less than half of the sterile syringes obtained from syringe exchange programs	4.7	8.7	4.6	6.4	

TABLE 1. Continued

	Barcelona	Madrid	Seville	Total
	(n = 364)	(n = 427)	(n = 200)	(n = 991)
Yes, at least half of sterile syringes obtained from syringe exchange programs	70.7	38.6	9.2	44.5
Lifetime experience of overdose				***
Suffered	35.4	22.4	9.0	24.6
Only witnessed	50.8	52.7	28.1	47.1
Neither suffered nor witnessed	13.7	24.6	62.8	28.3
Attendance at courses or meetings related with overdose prevention	11.1	3.1	0.5	5.5
Lifetime drug-dependency treatment	61.0	74.8	60.8	66.9

Statistical significance for the comparison among cities: ns Not significant.

p* < 0.05; *p* < 0.01; ****p* < 0.001.

^a refers to the last 12 months.

^b refers to methadone used outside of treatment.

route, after a period of abstinence, changing heroin supplier, and using methadone or opioids other than heroin. These nine factors represent the main risk factors for unintentional overdose identified in epidemiological studies or mentioned in the scientific literature. The criterion of selecting less than two risk factors as the cut-off point to define “limited knowledge” was established due to the small number of reasons cited by participants in the OEQ. The PCQ was not used to construct this indicator because it was defined based on the total number of overdose risk factors identified, and only the three most important reasons could be selected in the PCQ.

A bivariate analysis was made of the self-perceived reasons; statistically significant differences were evaluated with the Chi-square, rejecting the null hypothesis if *p* < 0.05. Based on various logistic regression models we identified the main factors associated with 1) “limited knowledge” of the risk factors for unintentional overdose and 2) identification in the OEQ or PCQ of the most frequent specific or grouped reasons; in the latter case, a model was developed for each reason analyzed. The variables significantly associated in the bivariate analysis were introduced into the models: age, sex, educational level, city of residence, length of heroin use, having suffered or witnessed overdoses, having received treatment to stop or control drug use, having attended courses or meetings related with overdose prevention and treatment, and variables with reference to the last 12 months before the interview (time in prison, frequency of heroin use, frequency of tranquilizer use, drug injection and obtaining sterile syringes in syringe exchange or distribution programs). Interactions with regard to city of residence were evaluated in logistic models. All the statistical analyses were made using SPSS ver. 11.5 for Windows.

RESULTS

General Characteristics of the Sample

The general characteristics of the sample have been described in detail elsewhere²⁶ and are summarized in Table 1. Injection was the usual route of heroin

TABLE 2. General reasons for opioid overdose mentioned in open-ended question or selected in pre-coded question (%)

Causes*	Cited in open-ended question (n = 920)	Selected in pre-coded question** (n = 979)	Cited in open-ended question or selected in pre-coded question (n = 983)	Most important cause cited in pre-coded question (n = 979)
Amount or characteristics of heroin	79.8	91.9	95.8	56.8
Use of a large amount of heroin or opioids	56.2	40.4	66.8	9.1
Use of heroin that is stronger or purer than usual	16.8	54.2	57.6	28.3
Use of adulterated or cut heroin	36.5	53.2	60.7	18.3
Change of heroin supplier	2.5	5.6	7.7	1.1
Use of heroin together with other drugs	38.3	60.2	65.3	24.1
Heroin and tranquilizers, without specifying in what order	22.9	16.9	33.7	4.2
Tranquilizers shortly before heroin	10.0	43.5	45.1	19.3
Heroin and alcohol, without specifying in what order	1.6	3.0	4.2	0.2
Alcohol before heroin	0.4	3.6	3.7	0.4
Heroin and cocaine	0.7	—	0.6	—
Heroin and another (or several) drugs	5.9	—	5.5	—
Use of heroin by the intravenous route	7.9	41.3	44.4	10.9
Use of heroin by the intravenous route in general	6.8	24.2	27.2	7.6
Injecting the whole dose at once or very quickly	1.1	22.3	22.8	3.4
Use of methadone or opioids other than heroin	0.9	—	0.8	—
Low tolerance to heroin	6.5	—	24.1	—
Use of heroin after a period of abstinence	6.4	22.6	24.0	5.8
Having recently begun heroin use	0.1	—	0.1	—
Constitutional, psychological or health causes	13.3	—	17.3	—
Predisposition, weakness, low defenses	7.9	—	7.4	—

TABLE 2. Continued

Causes*	Cited in open-ended question (n = 920)	Selected in pre-coded question** (n = 979)	Cited in open-ended question or selected in pre-coded question (n = 983)	Most important cause cited in pre-coded question (n = 979)
Other health problems	2.7	7.7	9.5	2.3
Psychological problems	1.8	—	1.7	—
Suicide attempt	1.3	—	1.2	—
Other causes	4.7	—	4.4	—
Meaningless causes	2.4	—	2.2	—

*There is no information from the pre-coded question for the causes marked with a hyphen (-), because they were not considered. The pre-coded question for the remaining reasons was formulated exactly as shown in the corresponding label in the table. If these labels are compared with those in Table 2, constructed from the verbatim responses in the open-ended questions, some slight differences in meaning may be found.

**Participants were asked to select the three most important reasons contributing to the overdose from a prepared list.

administration for most participants in Barcelona (59.3%), but this was not the case in Madrid (16.9%) or in Seville (1.0%), where the main route was pulmonary (“smoking the dragon”). However, a larger proportion of participants had injected heroin or other drugs in the last 12 months (75.4% in Barcelona, 47.3% in Madrid and 13.8% in Seville). In Seville, heroin and cocaine were usually mixed in the same dose (86.1% had routinely used this mixture in the last 12 months), whereas in Madrid and Barcelona, the use of heroin alone predominated. Cocaine use was very widespread in the three cities, frequently in the form of base or crack, and there was a tendency to use heroin and cocaine in the same chemical form and by the same route. In addition to cocaine, most participants used alcohol, cannabis or tranquilizers. Important differences among cities were seen in the prevalence of drug use, with generally higher prevalences in Barcelona. Most participants had at some time received treatment to abandon or control their drug use, and more than two of every three injectors (93.7% in Barcelona, 81.6% in Madrid, and 66.7% in Seville) had obtained most of their sterile syringes in the last 12 months through syringe exchange or distribution programs.

About 24.6% had suffered an opioid overdose sometime in their lives, with important differences by city (35.5% in Barcelona, 22.7% in Madrid and 9.0% in Seville). In addition, 8.1% had suffered the overdose in the last 12 months (15.4% in Barcelona, 4.4% in Madrid, and 2.5% in Seville). Some 67.2% initially stated they had personally witnessed an opioid overdose sometime in their lives (although 76% were not completely sure the drug was an opioid because they did not see and were not told what drug the person had taken), and 38.4% had witnessed this in the last 12 months. A few (5.5%) had attended specific courses or meetings related to overdose prevention or treatment, with important differences between cities.

Self-Perceived General Reasons for Overdose

The most frequently mentioned reasons in the OEQ, in decreasing order, were using a large amount of heroin, using highly adulterated heroin, using heroin together with tranquilizers (without specifying in what order the two were used), using heroin that was stronger and purer than usual, and using tranquilizers shortly

before heroin (Table 2). After grouping the reasons, it was seen that the responses of 79.8% of participants referred to the amount or purity of heroin, especially using a large amount of heroin or heroin that was purer than usual (65.1%), and 32.9% referred to concurrent use of tranquilizers and heroin. A much smaller number of participants mentioned reasons referring to concurrent heroin and alcohol or cocaine use, the form of heroin administration (injected use, very rapid injection), low tolerance to the drug, and constitutional, psychological or health factors. When participants were distributed by the number of unintentional overdose risk factors mentioned in the OEQ, it was seen that 64.6% cited fewer than two factors (limited knowledge). This proportion was higher in Seville (77.8%) than in Madrid (64.9%) or Barcelona (57.2%) ($p < 0.001$) (Fig. 1).

In the PCQ the most frequently selected reasons were quite similar to those in the OEQ. However, most reasons were selected much more frequently, except for use of a large amount of heroin or opioids and concurrent use of tranquilizers and heroin, without specifying the order. In fact, some reasons in the PCQ were selected many times more often than they were mentioned in the OEQ: injecting the whole dose at once or very rapidly (20.4 times), drinking alcoholic beverages shortly before using heroin (9 times), using tranquilizers shortly before using heroin (4.3 times), using the intravenous route (3.6 times), and using heroin after a period of abstinence (3.6 times) (Table 2).

In the analysis of the proportion of participants who identified each reason in the OEQ or PCQ, the smallest proportions were seen for use of methadone or opioids other than heroin (0.8%, although this was not included in the list of categories in the PCQ); concurrent use of alcohol and heroin (7.4%); constitutional, psychological or health reasons (17.3%); the use of heroin after a period of abstinence (24.0%); and the use of heroin by the intravenous route (44.4%). The largest proportions were seen for using heroin in large amounts (66.8%), using it together with tranquilizers (62.0%), using heroin that had been adulterated (60.7%) or that was purer than normal (57.6%) (Table 2).

There were important differences among cities in the frequency of reasons cited in the OEQ (Table 3). These differences were in the same direction in the PCQ.

FIGURE 1. Distribution of heroin users in Barcelona, Madrid and Seville by number of general overdose risk factors cited in the open-ended question (%). The nine main overdose risk factors were considered.

TABLE 3. General reasons for opioid overdoses and reasons for last opioid overdose suffered mentioned in open-ended questions by city of residence (%)

	General reasons for opioid overdose				Reasons for last opioid overdose suffered			
	Barcelona (n = 334)	Madrid (n = 410)	Seville (n = 176)	Total (n = 920)	Barcelona (n = 112)	Madrid (n = 88)	Seville (n = 15)	Total (n = 225)
Amount or characteristics of heroin	72.8	85.6	79.5	79.8**	41.8	61.4	53.3	50.2**
Use of a large amount of heroin or opioids	51.5	56.8	63.6	56.2*	27.9	44.3	40.0	35.1*
Use of heroin that is stronger or purer than usual	20.1	18.5	6.8	16.8***	10.7	14.8	6.7	12.0
Use of adulterated or cut heroin	28.1	46.8	28.4	36.5***	5.7	9.1	6.7	7.1
Change of heroin supplier	3.0	2.4	1.7	2.5	3.3	1.1	0.0	2.2
Use of heroin together with other drugs	55.1	30.5	24.4	38.3***	45.1	35.2	46.7	41.3
Heroin and tranquilizers, without specifying in what order	31.1	19.3	15.9	22.9***	24.6	20.5	13.3	22.2
Tranquilizers shortly before heroin	16.5	8.8	0.6	10.0***	14.8	10.2	0.0	12.0
Heroin and alcohol, without specifying in what order	1.8	1.5	1.7	1.6	4.1	2.3	13.3	4.0
Alcohol before heroin	0	1	0	0.4	0.0	1.1	0.0	0.4
Heroin and cocaine	0.3	0.7	1.1	0.7	4.9	2.3	13.3	4.4
Heroin and another (or several) drugs	8.1	2.7	9.1	5.9**	4.1	3.4	13.3	4.4
Use of heroin by the intravenous route	3.6	9.8	11.9	7.9**	3.3	12.5	20.0	8.0**
Use of heroin by the intravenous route in general	3.0	7.8	11.9	6.8***	2.5	6.8	20.0	5.3**
Injecting the whole dose at once or very quickly	0.6	2.0	0	1.1	0.8	5.7	0.0	2.7
Use of methadone or opioids other than heroin	0	1.2	1.7	0.9	1.6	3.4	0.0	2.2
Low tolerance to heroin	10.2	5.9	1.1	6.5***	14.8	15.9	13.3	15.1
Use of heroin after a period of abstinence	10.2	5.6	1.1	6.4***	13.9	13.6	13.3	13.8
Having recently begun heroin use	0	0.2	0	0.1	0.8	2.3	0.0	1.3
Constitutional, psychological or health causes	13.5	15.9	6.8	13.3**	14.8	9.1	20.0	12.9
Predisposition, weakness, low defenses	7.5	9.8	4.5	7.9	9.0	5.7	13.3	8.0
Other health problems	3.6	2.9	0.6	2.7	2.5	1.1	0.0	1.8
Psychological problems	1.5	2.4	1.1	1.8	3.3	1.1	6.7	1.3
Suicide attempt	1.2	1.2	1.7	1.3	3.3	1.1	6.7	2.7
Other causes	3.0	6.1	4.5	4.7	1.6	4.5	0.0	2.7
Meaningless causes	1.8	2.4	3.4	2.4	1.6	3.4	6.7	2.7

*p < 0.05; **p < 0.01; ***p < 0.001.

TABLE 4. Factors associated with identification of various general reasons for overdose in open-ended or pre-coded question

Reasons for overdose	Factors associated	Percent who identified this reason	OR	IC 95%
Use of a large amount of heroin or opioids	Age			
	25 years or less	71.4**	1.4	1.1–1.8
	More than 25 years old	63.6	1	
	Lifetime experience of overdose			
	Suffered	62.0**	0.6	0.4–0.9
	Only witnessed	65.7	0.7	0.5–1.0
Use of heroin that is stronger or purer than usual	Neither suffered nor witnessed	73.0	1	
	Sex			
	Male	59.6**	1.4	1.0–1.8
	Female	52.1	1	
	Lifetime drug-dependency treatment			
	Yes	60.2**	1.6	1.0–1.8
	No	52.0	1	
	Drug injection in last 12 months			
	Yes, at least half of sterile syringes obtained from syringe exchange programs	59.1	1.2	0.9–1.6
	Yes, less than half of sterile syringes obtained from syringe exchange programs	63.8	1.5	1.0–2.2
Use of adulterated or cut heroin	No	54.1	1	
	Frequency of heroin use in last 12 months			
	Less than weekly	72.3***	2.0	1.2–3.1
	1–4 days/week	55.5	0.9	0.6–1.1
	More than 4 days/week	61.4	1	
	City of residence			
Use of heroin together with tranquilizers or alcohol	Barcelona	47.5**	0.5	0.3–0.7
	Madrid	70.7	1.4	1.0–2.0
	Seville	63.5	1	
	Length of use			
	More than 5 years	67.7***	1.5	1.1–2.0
	5 years or less	54.8	1	
	City of residence			
	Barcelona	74.2***	2.5	1.6–3.8
	Madrid	62.9	1.3	0.9–2.0
	Seville	47.7	1	
	Lifetime experience of overdose			
	Suffered	78.5***	3.0	1.9–4.6
	Only witnessed	68.0	2.0	1.4–2.8
	Neither suffered nor witnessed	44.6	1	
	Frequency of heroin use in last 12 months			
	More than 4 days/week	66.1**	2.2	1.4–3.5
	1–4 days/week	65.0	2.0	1.2–3.2
	Less than weekly	50.9	1	
	Lifetime drug-dependency treatment			
	Yes	69.1	1.6	1.2–2.2
	No	53.9	1	

TABLE 4. *Continued*

Reasons for overdose	Factors associated	Percent who identified this reason	OR	IC 95%
Use of heroin by the intravenous route	Drug injection in last 12 months			
	Yes, at least half of sterile syringes obtained from syringe exchange programs	56.1***	2.3	1.7–3.2
	Yes, less than half of sterile syringes obtained from syringe exchange programs	39.9	1.3	0.9–2.0
	No	31.0	1	
	City of residence			
	Barcelona	31.4***	0.6	0.4–0.9
	Madrid	50.9	1.2	0.8–1.7
	Seville	53.8	1	
	Age			
	25 years or less	41.3**	1.5	1.1–1.9
	More than 25 years old	48.5	1	
Low tolerance to heroin	City of residence			
	Barcelona	32.2***	5.2	3.0–9.0
	Madrid	24.2	3.1	1.8–5.4
	Seville	9.1	1	
	Age			
	25 years or less	27.7**	1.8	1.3–2.5
	More than 25 years old	19.2	1	
	Frequency of tranquilizer use in last 12 months			
	Not used	18.9**	1.0	0.6–1.6
	Less than weekly	22.3	1.0	0.7–1.5
Constitutional, psychological or health reasons	1–4 days/week	31.3	1.7	1.1–2.5
	More than 4 days/week..	23.2	1	
	Educational level			
	Primary or lower education	20.7**	1.5	1.0–2.1
	Secondary or higher education	13.2	1	
	City of residence			
	Barcelona	16.1**	1.5	
	Madrid	21.8	2.3	0.8–2.6
	Seville	9.6	1	1.3–4.0
	Length of use			
	5 years or less	15.9	0.7	0.5–1.0
	More than 5 years	20.8	1	

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Self-Perceived Reasons for Overdoses Suffered by Participants

The most frequent reasons for overdoses suffered by participants that were cited in the OEQ were, in decreasing order of frequency, using a large amount of heroin, using heroin together with tranquilizers (without specifying the order), using heroin after a period of abstinence or very occasionally, using very pure heroin, and using tranquilizers shortly before heroin (Table 3). When the reasons were grouped, it was seen that 50.2% of participants mentioned reasons related with the amount or

characteristics of heroin (especially—44.1%—reasons related with using a large amount of heroin or very pure heroin), and 41.3% cited reasons related with the concurrent use of heroin and other drugs (especially—33.8%—tranquilizers and heroin). When participants were asked about the most important reason for the overdose, the order of the specific and grouped reasons was very similar to the preceding, although in this case the use of tranquilizers shortly before heroin was more important and came in third place. In comparing the general reasons for overdose with the reasons for overdoses suffered by the participant, it was seen that, in the former case, participants more often mentioned reasons related with the amount or characteristics of heroin (especially using heroin that had been cut or adulterated), whereas the opposite occurred with the use of heroin after a period of abstinence (Tables 2 and 3). A comparison by city of the frequency of reasons for overdoses suffered by participants showed differences in the same direction as described in the general reasons for overdose.

Factors Associated with Self-Perceived General Reasons for Overdose

In the logistic regression model the factors associated with limited knowledge of overdose risk factors were residence in Seville (OR for Seville vs. Barcelona = 3.0; 95% CI = 1.9–4.7) or Madrid (OR for Madrid vs. Barcelona = 1.3; 95% CI = 1.0–1.8), not having attended courses or meetings related with overdose treatment or prevention (OR = 1.9; 95% CI = 1.1–3.4), and secondary or higher educational level (OR = 1.4; 95% CI = 1.0–1.9). No interaction terms with regard to city of residence were retained in the model.

With respect to the factors associated with the identification of certain specific or grouped reasons in the OEQ or PCQ, the factor retained by the largest number of models was the city of residence, which was significantly associated with identification of the following reasons for overdose: use of heroin together with tranquilizers or alcohol, after a period of abstinence, by the intravenous route; highly adulterated heroin; and constitutional, psychological or health reasons (Table 4). There was also a rather strong association between identification of intravenous use of heroin as a reason for overdose and not having injected in the previous 12 months and between identification of concurrent use of heroin and tranquilizers or alcohol as a reason for overdose and having used heroin weekly during the previous 12 months or ever having suffered or witnessed an overdose (Table 4). No interaction terms with regard to city of residence were retained in the models, except for use of highly adulterated heroin. In this case the association with frequency of heroin use disappeared and was replaced with the interaction term city of residence by frequency of heroin use, specifically, living in Madrid by using heroin less than weekly (OR vs. using heroin more than 4 days/week = 4.5; 95% CI = 1.1–18.8) and living in Madrid by using heroin 1–4 days/week (OR vs. using heroin more than 4 days/week = 3.8; 95% CI = 1.1–13.8).

DISCUSSION

The main findings of this study are as follows: 1) In 2001–2003 most young heroin users in the cities studied still did not have sufficient knowledge of the overdose risk factors: 64.6% were unable to name more than one risk factor in the OEQ. 2) Some overdose risk factors, such as using a large amount of heroin or heroin that is purer than usual and using heroin and tranquilizers together were known quite

frequently. In contrast, only a small proportion of users recognized as reasons for overdose certain risk factors widely recognized by the scientific community, such as concurrent use of heroin and alcohol, using heroin after a period of abstinence or by the intravenous route, and using methadone together with heroin or other depressants (benzodiazepines or alcohol). Furthermore, there was rather widespread belief in what is generally considered an erroneous idea—that highly adulterated heroin as such was a risk factor for overdose. 3) The city of residence was strongly associated both with limited knowledge of the overdose risk factors and with whether or not various specific risk factors were identified, such as concurrent use of heroin and tranquilizers or alcohol; low tolerance to heroin; constitutional, psychological or health reasons; and use of highly adulterated heroin or use of the intravenous route. 4) Limited knowledge (naming fewer than two risk factors) was associated with not having attended specific courses or meetings related with overdose prevention or treatment, but it was not associated with having undergone drug-dependency treatment or having used free or subsidized services for the exchange or distribution of sterile syringes.

The fact that most heroin users have poor knowledge of the risk factors for overdose strongly limits or impedes the adoption of appropriate precautions or measures to avoid overdoses in this population. It is surprising that this type of situation continues to exist in a country like Spain, where in the last decades heroin has been responsible for thousands of deaths from overdose, especially among males in urban areas, and where major investments have been made in treatment and harm reduction programs for these users.

It is commonly accepted that overdose is the result of introducing more opioids in the organism than the user can tolerate at that time¹²; therefore, using heroin in larger amounts or that is purer than usual could contribute to the cause of many overdoses. It is not surprising, then, that as in other studies,^{22–24,32} this factor was by far the most frequent reason for overdose recognized by the young heroin users in the cities studied. In fact, 85.1% identified it in the OEQ or PCQ referring to overdose in general. Previous studies have found that use of a larger than usual amount of heroin greatly increases the risk of overdose,^{15,33} although there is also evidence that the blood concentration of morphine is relatively low in most overdose fatalities,¹² especially when other respiratory depressants are present. Furthermore, there is only moderate evidence of a relation between fluctuations in heroin purity and overdose.¹⁴

Another widely accepted risk factor for overdose is the use of heroin together with other central nervous system depressors such as tranquilizers (mainly benzodiazepines) and alcohol.^{1,4,11–15,33–35} The participants in this study identified the use of tranquilizers together with heroin as an important reason for overdose more frequently than using heroin by the injected route or after a period of abstinence; however, a large proportion (38%) of them did not recognize this reason. An interesting issue for discussion is whether the order in which tranquilizers and heroin are taken affects the risk of overdose. In the pilot study, some heroin users said that the danger was in using the tranquilizer before heroin and not their concurrent use in the opposite order. In the final study, 10% of participants spontaneously mentioned use of a tranquilizer shortly before heroin as a risk factor for overdose in the OEQ, and 43.5% selected this reason in the PCQ. The proportion of persons in the OEQ who mentioned the concurrent use of heroin and tranquilizers as an overdose risk factor, without specifying the order of use, was 22.9%, and this factor was selected in the PCQ by 16.9% of participants. Although this

issue has not been explored in the scientific literature, we believe it is reasonable to test this hypothesis because the plasma elimination half-life of heroin is very short, which is not the case with the tranquilizers usually consumed by heroin users in Spain and other countries, such as alprazolam, flunitrazepam or diazepam.⁸

The extremely large proportion of participants who did not identify the use of heroin together with alcohol as a reason for overdose (92.6%) was surprising, despite the many studies that have detected this risk factor.^{12-14,36-38} Likewise, most participants (75.9%) did not recognize the use of heroin in situations of low tolerance as important general reasons for overdose (for example, after a period of abstinence). This cause has been recognized in numerous studies^{13,14,16,39-42} and is consistent with the fact that most overdose fatalities have relatively low blood concentrations of morphine.¹² The low perception of risk associated with the loss of tolerance and the high frequency with which this situation occurs among participants (in the last 12 months 44.1% had abstained from heroin for more than 30 consecutive days and 7.1% for 16–30 days) suggest that this factor may play an important role in the overdoses produced in the cities studied. That most users have a better knowledge of the risk of using more or purer heroin than usual than they do of the risk of loss of tolerance is consistent with the results of other studies^{22-24,32} and may lead users to take more precautions in relation with the former factor than the latter.²²

Many young heroin users in the cities studied are also not conscious of the high risk of overdose from using heroin by the intravenous as opposed to other routes of administration (55.6% did not identify this factor), especially injectors who had not been in contact with syringe exchange or distribution programs, those who had been in prison for a long time and those who lived in Barcelona. This is of great concern because heroin injection is known to be associated with a much higher risk of overdose than other routes,^{1-4,10,11,13,14,35,43} especially when combined with a situation of possible loss of tolerance (sporadic heroin injections).^{13,44} In recent years, overdose mortality in Spain has decreased more slowly than expected,⁷ during a time of expanded methadone maintenance treatments and rapid reduction in injection as the usual route of heroin administration.⁸ The explanation for this slow decrease could be that a considerable proportion of heroin users continue to inject sporadically, with little or no awareness of the risk of overdose involved in this behavior. In fact, 70.7% of participants who were not regular heroin injectors in the last 12 months had injected some drug during this period (38.5% in Barcelona, 31.9% in Madrid and 12.9% in Seville).

Less than 5% of participants mentioned psychological problems or suicide as reasons for overdose suffered. This is consistent with recent evidence suggesting that only a small proportion of overdoses are deliberate,^{14,33,45} although symptoms of depression seem to be more common among users who have suffered an overdose.⁴⁶ A larger proportion (17.4%) of participants attributed the overdoses to constitutional or health reasons, often verbalized as “predisposition,” “weakness” or “low defenses.” It has been hypothesized that poor general health status, in particular, liver or lung disease, could increase the risk of overdose,¹² and there is some evidence of an increased risk of overdose with long-term HIV infection.^{10,11,13,43} However, the words participants used most frequently to refer to these reasons cannot be considered as established overdose risk factors. Thus, this reason was not included in the list of overdose risk factors used to define “limited knowledge.”

Participants did not perceive methadone use to be an important reason for overdose. In fact, less than 1% identified the use of methadone or opioids other than heroin as a general reason for overdose, although this reason was not included

in the list of categories in the PCQ, which undoubtedly contributed to its underestimation. In recent years there have been increased reports of methadone involvement in deaths from overdose,^{19,47,48} although some studies do not support this relation.⁴⁹ In fact, the proportion of overdose deaths in Spain in which the toxicological reports indicated the presence of methadone increased from 15.8% in 1996 to 41.7% in 2002, although in over 95% of cases it was detected together with heroin.⁸ In this respect, our study found a surprisingly high level of “street methadone” use, especially in Seville (57% in the last 12 months), but also in Barcelona (32%) and Madrid (29.7%). The concurrent use of heroin and methadone increases the risk of overdose, yet very few heroin users listed this as a reason for overdose. Consequently, in Spain the role of street methadone in the risk of overdose and in overdose education should be emphasized. On the other hand, the possible effect of street methadone in increasing the risk of overdose should be assessed together with the evidence that methadone maintenance programs are a very important protective factor for overdose mortality.^{4,10,50,51}

As previously noted, participants frequently identified the use of highly adulterated heroin as a reason for overdose. This reason was not considered in the definition of sufficient/insufficient knowledge of overdose risk factors because studies indicate that dangerous adulterants are rarely found in the syringes or bodies of persons dying from overdose,¹⁴ and this factor is currently practically ruled out as a cause of overdose.¹² However, as is explained below, some users may perceive the use of adulterated/cut heroin as a risk factor for overdose because it affects their ability to estimate the proper dose. Such an interpretation could be useful knowledge as it reinforces the need to have stable heroin suppliers or to test the purity of heroin before using the whole dose.

The results of this study indicate that the factor most strongly associated with limited knowledge of the reasons for overdose was the city of residence. Specifically, users in Seville most frequently had limited knowledge. We also detected important differences in knowledge of the various specific reasons for overdose by city of residence, especially for low tolerance to heroin, but also for using heroin together with tranquilizers or alcohol, use of adulterated or cut heroin, use of heroin by the intravenous route, and constitutional, psychological or health reasons. The differences among cities cannot be explained by unequal exposure to syringe exchange/distribution programs or to drug-dependency treatment or by different patterns of drug use, since the logistic models controlled for these factors. Nor could they be explained by unequal direct exposure to specific programs for overdose prevention, although given that these programs seem to be effective, there may be an indirect effect (ecological effect) not controlled for in the models that would partly explain the differences among cities.

Limited knowledge of the general reasons for overdose was associated with not having attended courses or meetings related with overdose prevention or treatment (OR = 1.9). Other factors, such as the route of heroin administration (injector/non-injector), having received treatments to stop or control drug use, or having used free or subsidized services for sterile syringe exchange or distribution, were not independently related with sufficient/limited knowledge of overdose. The weak association between limited knowledge of overdose risk factors and higher educational level was unexpected and difficult to explain but may suggest a state of unfounded or excessive confidence in one's own ability to identify the causes of overdose from experience or a resistance to learning from professionals or services on the part of users with a higher level of education.

The data in Table 4 suggest that knowledge of a certain risk factor may be driven by exposure to this particular risk factor and the individual drug user's risk profile. For example, it is understandable that injectors are less likely to mention injection as a risk factor for overdose because within this group factors other than injection will differentiate those who overdose from those who do not. Also, some injectors do not recognize alternatives to injection or injection as a modifiable risk behavior. Similarly, daily heroin users may have more reliable sources of heroin than sporadic users and, thus, would be less likely to cite the use of adulterated heroin as an overdose risk factor. In fact, this was the case in the study sample, especially in Madrid. It is also probable that users have a certain tendency to justify their own conduct (for example, using heroin by the intravenous route) when asked to identify the reasons for overdose. Accordingly, when interventions aimed at overdose education and prevention are designed, differences in exposures and risk profiles among cities and user subgroups should be taken into account.

Taken as a whole, these findings suggest a strong need to develop informational and educational programs (workshops, meetings, training programs) to make users more aware of the overdose risk factors and to eliminate groundless beliefs such as heroin adulteration being the reason for overdose. It should be emphasized in this regard that few study participants had been exposed to these types of programs: Only 11.1% in Barcelona, 3.1% in Madrid, and 0.5% in Seville indicated that they had received courses to prevent or treat overdose, although 52.3 to 64.8% said they would attend such courses if it was proposed to them. On the other hand, the geographical differences in the knowledge of different reasons suggest that the target groups for these programs, their content, and most certainly the communication strategy, should be adapted to the local context and different risk profiles of user subgroups. In this respect, in the three cities studied it is important to emphasize the role in the risk of overdose of such factors as use of the intravenous route, situations with low tolerance to heroin, use of heroin together with alcohol, and use of methadone concurrently with heroin, benzodiazepines or alcohol. However, different factors may need to be emphasized depending on the city. For example, in Barcelona the role of the intravenous route should be emphasized more than in Seville or Madrid, whereas low tolerance to heroin is a more important risk factor in the latter two cities. Moreover, in Madrid it should be stressed that using adulterated/cut heroin is a considerably less important risk factor for overdose than perceived by users. It is also important that other services for drug users (mainly drug-dependency treatment services and syringe exchange programs) should include effective advice to make users more aware of the factors and situations that increase the risk of overdose, since our results show that these services are not currently effective in this regard.

An advantage of this study is that it was carried out in a large sample of young heroin users in three cities. The study also permitted a highly detailed exploration of the perceived reasons for overdose by using both OEQs and PCQs. However, some limitations must be taken into account when interpreting the results. In the first place, it is not known to what extent the results can be generalized to all heroin users in the cities studied or to those in Spain as a whole, since we used non-probabilistic sampling. The sample included a larger proportion of young and of occasional users than some previous studies in samples recruited in treatment centers or other areas.^{8,25} However, the results regarding patterns of drug use are quite consistent with these studies, which suggests that the differences among cities are not due to the recruitment mechanisms used. It should also be kept in mind that the reasons

for overdose expressed by users are the result of experiences and information received throughout their drug-use careers and of the myths and stereotypes that circulate within their social networks. It would have been interesting to explore possible differences in the knowledge of risk factors among recruitment networks. However, such an analysis was difficult because of the very small number of participants in most networks. Consequently, it is possible that this sampling approach might artificially affect the findings of the study. Furthermore, in the case of overdoses suffered, the events may have occurred long before the interview, thus it may have been difficult for participants to clearly remember the reasons. Nevertheless, we found no important differences in the reasons cited by those who had suffered the overdose recently (in the last 24 months) and those who had suffered it before that time.

The definition of “limited knowledge of risk factors for unintentional overdose” as the mention of less than two of nine main risk factors for overdose is arbitrary. However, it fits well with the multifactorial etiology of opioid overdose. Individual heroin users with well-defined risk profiles (for example, non-injection heroin users who use heroin only with alcohol) might consider themselves to be sufficiently protected against overdose by knowing and avoiding the main risk factors to which they are currently exposed (in the example, the concurrent use of heroin and alcohol). However, such a belief is dangerous because risk profiles are often unstable and frequently change (the heroin user could start to inject heroin one day and would not be aware of exposure to a very high risk of overdose). Furthermore, the definition seems quite robust with regard to the data analyzed. In fact, the factors associated with “limited knowledge” did not change when the term was defined as the mention of fewer than two of five main risk factors for overdose.

In conclusion, most young heroin users in Barcelona, Madrid and Seville do not have sufficient knowledge of overdose risk factors. Residence in Seville and not having attended courses or meetings on overdoses were significantly associated with limited knowledge of these risk factors, after adjusting for other factors. The most frequently unknown risk factors for overdose were the use of heroin by injection, after a period of abstinence, or together with alcohol and the use of methadone together with heroin or other depressants, with important differences between cities. Furthermore, there was rather widespread belief that highly adulterated heroin was a risk factor for overdose, especially in Madrid. Consequently, specific informational or educational programs adapted to the local context are critically needed.

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