Willingness of patients with SUD to participate in research: prevalence and associated factors

Disposición para participar en investigación en población adicta: prevalencia y factores asociados

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Abstract

Greater attention is focusing on the motivations of subjects recruited for research protocols, especially in vulnerable populations. Although addiction is a highly stigmatized condition, very little research has focused on the factors influencing the decision to participate of patients with an addiction. Our aim is to gather further evidence in relation to the motivations of people with Substance Use Disorders (SUD), comparing their reasoning and willingness to participate in a hypothetical research study of 53 subjects with DSM-5 diagnoses of SUD and 50 controls. Responses on the MacArthur Competence Assessment Tool for Clinical Research were documented and correlated with several variables. There were no significant differences in willingness to participate in research and reasons for doing so between SUD and controls. Among SUD subjects, 59% mentioned altruism, 53.8% expected therapeutic benefits, and 43.6% desired to help others; none mentioned money. Of those patients with SUD who refused to participate in research, 69.2% cited aversion and 46.2% mentioned risk. Willingness to participate was correlated with higher computer literacy and better cognitive performance. In the multivariate analysis, aversion was a significant predictor of willingness to participate in research. When research is not related to their diagnosis, the motivations of SUD and controls are similar and flowed logically from the study. However, elements associated with therapeutic misconceptions were also evident. Therefore, negative views about the motivations of SUD subjects' participation in research are unfounded. Consequently, to improve study recruitment, assessments may be targeted to specific vulnerabilities rather than to diagnoses.

Keywords: Addictions; Research ethics; Motivation; Decision-making.

Resumen

Cada vez se presta más atención a las motivaciones de las personas reclutadas para ensayos clínicos, especialmente si pertenecen a colectivos vulnerables. Aunque la participación en investigación de las personas con trastorno por uso de sustancias (TUS) suscita estereotipos negativos, muy pocos estudios se han centrado en los factores que influyen en la misma. Nuestro objetivo es analizar sus motivaciones comparando las razones y la disposición a participar en un ensayo hipotético de 53 pacientes con diagnósticos DSM-5 de TUS y 50 controles. Las respuestas que dieron a la entrevista MacArthur Competence Assessment Tool for Clinical Research se correlacionaron con diversas variables. No encontramos diferencias significativas entre ambas poblaciones en términos de motivaciones y disposición a participar. El 59% de la población TUS mencionó altruismo, un 53,8% esperaba beneficio terapéutico, y el 43,6% deseaba ayudar a otros. De los pacientes con TUS que rechazaron participar, el 69,2% alegó miedo y el 46,2% incomodidad por los riesgos. La disposición a participar se relacionó con un mayor nivel cognitivo y de alfabetización informática. En el análisis multivariante, la aversión a la investigación permaneció como factor predictivo significativo de la disposición a participar. Cuando la investigación no está relacionada con su diagnóstico, las motivaciones de la población TUS son similares a las de los controles y se deducen lógicamente del estudio, aunque también se evidenciaron elementos de "error terapéutico". Por consiguiente, las visiones negativas sobre las motivaciones de los TUS como participantes en investigación son infundadas. Para mejorar el reclutamiento, las valoraciones deben dirigirse a vulnerabilidades especificas en lugar de al diagnóstico.

Palabras clave: Adicciones; Ética en investigación; Motivación; Toma de decisiones.

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Biomedical research is critical for advancing scientific knowledge and for improving patient treatment. The success of research is dependent on recruitment rates and sufficient participant retention. Recent studies are focusing on the motivations and willingness to participate in research (Geppert, Candilis, Baker, Lidz & Appelbaum, 2014; Lawton et al., 2016; Tromp, Zwaan & van de Vathorst, 2016), especially in vulnerable or marginal populations (Barrat, Norman & Fry, 2007; Candilis, Geppert, Fletcher, Lidz & Appelbaum, 2006). Although addiction is a stigmatised condition that raises doubts about the real motivation for contributing toward scientific progress, a review of the scope of research on addictions (Nogué & Miró, 2015) detects very few studies that focus on factors influencing participation (Barrat et al., 2007; Fry & Dwyer, 2001).

Previous studies with the general population have explored the reasons given by research participants: access to information, monetary gain, curiosity, desire to help others and contribute toward science (Candilis et al., 2006; Seelig & Dobelle, 2001). In addition, negative factors, like fear and uneasiness with regards to the procedures, may act as barriers to participation or decrease adherence in studies (Ammassari et al., 2002; Brintnall-Karabelas et al., 2011). The extent to which these findings may be extrapolated to the SUD population is unknown. The few studies with people with SUD in this regard have explored the role of economic incentives in research (Barrat et al., 2007; Fry et al., 2001). Some researchers argue that, from an ethical perspective, receiving monetary payment for participation in research could invalidate informed consent (Fry, Hall, Ritter & Jenkinson, 2006a; Misra, Socherman, Park, Hauser y Ganzini, 2008). Participants might take risks which they would not assume in the absence of the incentive, and this would nullify the principle of justice by conditioning, more so, socioeconomically disadvantaged groups, like those with SUD (Carter & Hall, 2012; Dunn, Kim, Fellows & Palmer, 2009).

Another reason for trying to better understand the reasons for participating in research of the SUD population is related to the prevalence of negative stereotypes about addiction (Morera, 2000) and the assumptions about this group, even by professionals offering treatment (Barrat et al., 2007).

To the extent of our knowledge, no studies using the Spanish population review those factors which encourage or deter SUD patient participation in research. Detecting this population's motivations will enable professionals to define the aspects and information these patients consider important and relevant for decision-making. This will allow for designing the recruitment and informed consent process from the perspective and needs of patients with SUD. The purpose of this study is to provide greater evidence as to why SUD subjects participate in research in our setting.

Method

Study type

This is a transversal study, approved by our hospital's Research Ethics Committee (University Hospital of Cartagena).

Participants

This study derives of another that compares the capacity for participating in research of the SUD population. The complete details may be consulted separately (Morán-Sánchez, Luna, Sánchez, Aguilar & Pérez-Cárceles, 2016). This study focuses on the motivations and willingness to participate of 53 patients treated for the use of alcohol and/or illegal substances at a Drug Addiction Treatment Centre and 50 controls without a psychiatric disorder at a Health Centre. All of those patients with an ongoing participation at the study centres during a 4-month period were invited to participate. The participants included outpatients with DSM-5 and SUD diagnoses, and controls with diagnoses of hypertension, diabetes mellitus or other chronic illnesses. Inclusion criteria were: (a) minimum age of 18 years, (b) diagnoses of the study's target disorders, (c) fluent Spanish speaker, (d) score of 20 or higher in the Spanish version of the Mini-Mental State Examination: MEC (Lobo et al., 1999), and (e) signing the voluntary consent.

Controls were excluded if they (a) met current criteria for SUD or other DSM-5 diagnoses (American Psychiatric Association, 2014), (b) were currently patients of the Mental Health Centre or Drug Addiction Treatment Centre, or (c) were receiving psychiatric treatment through their primary care physician.

Users were excluded if they showed signs of intoxication or drug withdrawal symptoms when requesting their consent.

Measures

Participant information was collected using a questionnaire designed to gather demographic and clinical variables. The level of functioning of the SUD population was evaluated using the Global Assessment Scale (Endicott, Spitzer, Fleiss & Cohen, 1976), and the severity of their symptoms was evaluated using the Clinical Global Impression Scale (Guy, 1976).

Motivations and willingness to participate in research were collected from the responses obtained in the Spanish version of the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) scale (Baón, 2013). This instrument is a semi-structured interview adapted to the elements of a specific research protocol, and evaluates the 4 most well-known dimensions of decision-making capacity: (a) *understanding* of information; (b) *appreciation* of consequences, given each patient's circumstances; (c) *reasoning* for deciding on whether or not to participate, and (d) *ability to express a choice* with regards to project participation

(Appelbaum & Grisso, 2001). Applying the MacCAT-CR interview entails providing information about the study and requesting the subjects to consider participating, followed by questions that evaluate their capacity, scored between 0-2, with a higher score reflecting better performance. The Understanding scale contains thirteen questions, the Appreciation scale contains three questions, the Reasoning scale contains four questions and the Ability to express a choice scale contains just one question. This instrument has been widely used in research, and is described in detail separately (Appelbaum et al., 2001). The subjects' willingness to participate in the hypothetical study was obtained from their responses to the Ability to express a choice subscale (*"Now that you have had more time to think about this, I'd like to ask you again if you think it is more likely that you will participate, or not, in this study"*). Motivations to participate in research were obtained from the responses to the Reasoning subscale (*"So, you think that you will decide to participate/not participate in the study. What makes this the best option for you?"*) that were collected and coded, according to their content.

The hypothetical consent designed for this study described a randomised clinical trial using a placebo of an experimental compound for headache treatment. The form described blood extraction and the risk of non-vital side effects. Also, information was given on the voluntary nature of participation, the inability to guarantee any personal benefit and the possibility of withdrawing.

Procedures

Once the participants signed their informed consent, the MEC-30 was implemented to evaluate their cognitive level, excluding those with advanced deterioration. Afterward, the hypothetical project was read to them aloud, and the MacCAT-CR interview was administered and scored in accordance with the criteria set forth in its manual.

Statistical analysis

Statistical analysis was performed using the SPSS (version 19) package. Before the analysis, we verified the distribution of continuous variables to check their normality. The differences in ordinal and continuous data were analysed using the Mann-Whitney *U* test. For differences between categorical variables, we used the Pearson χ^2 or the Fisher exact test for nonparametric data.

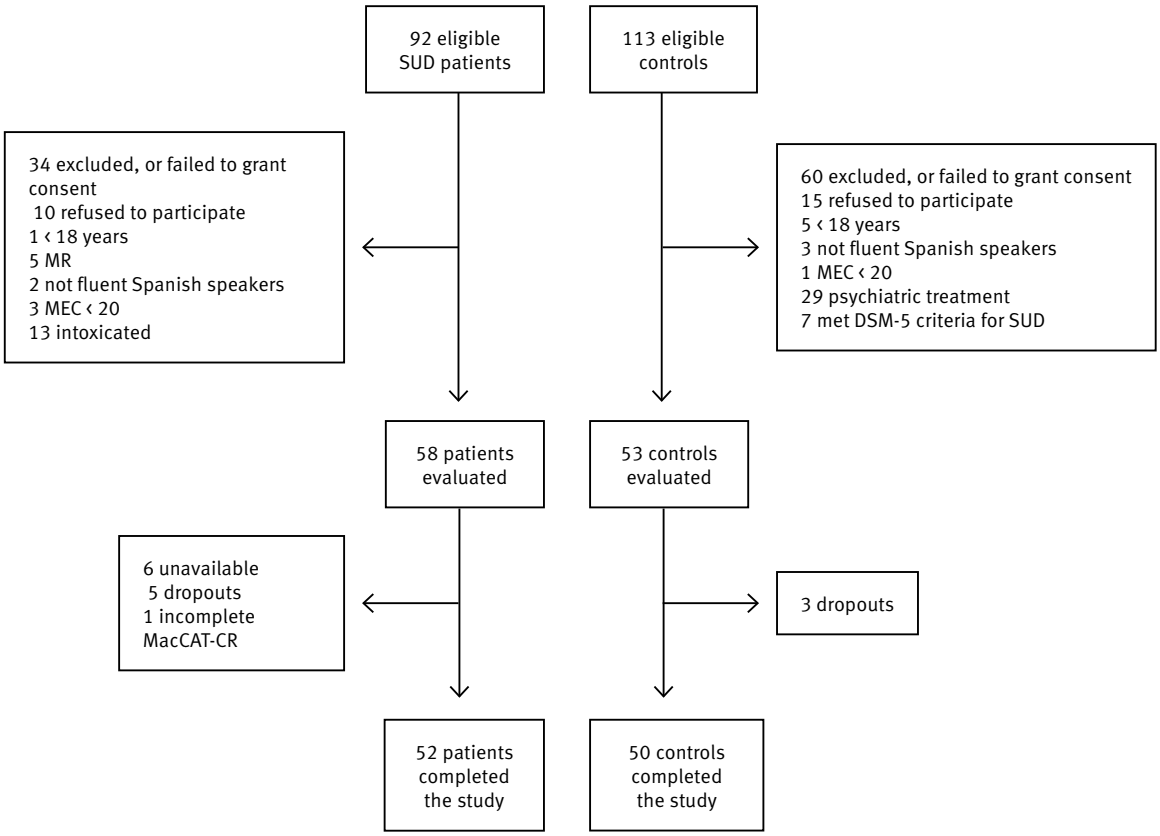

Figure 1. Participant inclusion flow chart

Note. SUD: Substance Use Disorder; MEC: Mini-Mental State Examination; MR: mental retardation; MacCAT-CR: MacArthur Competence Assessment Tool for Clinical Research

Table 1. *Study participant baseline characteristics*

	SUD (*n* = 53)	**Control** (*n* = 50)	**p**
Age (Average in years -*SD*-)	42.9 (*11.9*)	48.6 (*11.9*)	.037[b]
Females (%)	28.3	62	‹.001[a]
Marital status (%)			‹.001[a]
Married/cohabitation	32.1	82	
Never married	41.5	6	
Previously married	26.4	12	
Type of cohabitation (%)			‹.001[c]
Alone	15.1	12	
With own family	45.3	88	
With family of origin/foster family	39.6		
Level of education (%)			‹.001[a]
Primary	58.2	20	
Secondary	32.1	20	
University	9.4 5	40	
Employment status (%)			‹.001[c]
Employed	20.8	84	
Unemployed	45.3	2	
Retired	13.2	14	
Disabled	20.8		
Previous research study (%)			‹.001[a]
Yes	1.9	46	
No	98.1	54	
Computer literacy (%)			‹.001[a]
Yes	81.1	96	
No	18.9	4	
MEC (range, 0-30) (Average score -*SD*-)	28.2 (*4.2*)	29.6 (*0.9*)	‹.001[b]

Note. SD: standard deviation; SUD: Substance Use Disorder; MEC: Mini-Mental State Examination. [a] Pearson χ 2. [b] Mann-Whitney U. [c] Fisher's statistic.

To identify those factors that predictor willingness to participate in research, we performed a logistic regression analysis, calculating the Odds Ratios (OR) and the 95% confidence interval (CI). The multivariate analysis included statistically significant independent variables from the univariate analysis, and others that, despite being nonsignificant statistically, were clinically relevant. This study's sample size was the maximum possible obtained during the recruitment period. A minimum of 10 cases for each possible value of the response variable was considered sufficient for the logistics regression analysis, according to the calculation formula proposed by Peduzzi (Ortega & Cayuela, 2002). In line with recommendations given in literature, we used the method of directly introducing the variables to obtain a model with variables directly related with the dependent variable (Aguayo, 2010; Nuñez, Steyerberg & Nuñez, 2011).

The model's validity was tested using omnibus tests of coefficients, the Cox-Snell and Nagelkerke R square tests and the Hosmer-Lemeshow test. A significance level of .05 was used for all analyses.

Results

Of the study's 205 eligible subjects, 103 were excluded or unavailable to participate for various reasons. Figure 1 shows the patients' flow chart during the study.

Table 1 displays the study participants' baseline characteristics.

The 53 patients with SUD had the following diagnoses (not shown): 45.3% (n = 24) had alcohol or cannabis use disorder, 18.9% (n = 10) used cocaine and 35.8% (n = 19) used alcohol and another substance. THC users were younger, 32.92 years (*SD* = 12.72), and alcohol users were older, 51.67 years (*SD* = 7.63); χ *2* (2, N = 53) = 11.81, p =.003. Illness duration was also longer in the alcohol user group, 19.67 (*SD* = 13.26) than in the remaining groups (7.42 years (*SD* = 7.13) in THC users; 9.80 years (*SD* = 6.56) in cocaine users and 18.11 years (*SD* = 9.13) in users of alcohol and another substance; χ *2* (2, N = 53) = 6.45, p = .04. The remaining variables studied did not have statistically significant differences.

Willingness to participate in research and related factors

Of the SUD group and the control group, 75% (n = 39) and 78% (n = 39), respectively, were willing to participate in the hypothetical research project, without statistically significant differences between both groups, χ *2* (1, N = 102) = 7.21, p =.721.

Table 2 describes the characteristics of SUD patients according to their willingness to participate in the hypothetical research project. We found significant differences in MEC scores (Z = -1.99, p = .047) and in computer literacy level (87% high computer literacy level among those willing to participate *vs* 61.5% among those unwilling to participate; χ *2* (1, N = 52) = 4.13, p =.042). There were no statistically significant differences between patients willing and unwilling to participate for the remaining variables studied (sociodemographic, clinical and decision-making capacity).

Motivations for participating in research.

The responses to the MacCAT-CR Reasoning subscale on the patients' motivations for deciding to participate, or not, in a study, were classified into six categories, shown in Table 3:

a. Altruism/desire to contribute toward scientific progress.
b. Expectation of personal gain.
c. Desire to help others.
d. Uneasiness concerning side effects.
e. Aversion to the study.
f. Other reasons, different from the above.

Of the patients with SUD, 59% (n = 23) were willing to participate in the hypothetical study, mentioning altruism as their motivation, 53.8% (n = 21) expected a personal gain and 43.6% (n = 17) mentioned the desire to help others. The reason most frequently mentioned for refraining from

Table 2. *Characteristics of SUD population according to willingness to participate in the study*

	Willingness to participate		**p**
	Yes (*n* = 39)	No (*n* = 13)	
Age (Average in years -*SD*-)	44.1 (*11.1*)	40.5 (*13.9*)	.533[c]
Females (%)	35.9	7.7	.078[b]
Marital status (%)			.614[b]
Married/cohabitation	33.3	23.1	
Never married	38.5	53.8	
Previously married	28.2	23.1	
Type of cohabitation (%)			.641[b]
Alone	12.8	16.7	
With own family	48.7	62.5	
With family of origin/foster family	38.5	20.8	
Level of education (%)			.263[b]
Primary	59	53.8	
Secondary	28.2	46.2	
University	12.8		
Employment status (%)			.947[b]
Employed	23.1	15.4	
Unemployed	43.6	46.2	
Retired	12.8	15.4	
Disabled	20.5	23.1	
Previous research study (%)			1.00[b]
Yes	2.6		
No	97.4	100	
Computer literacy (%)			.042[b]
Yes	87.2	61.5	
No	12.8	38.5	
Psychiatric diagnosis (%)			.166[c]
Psychotic disorder	12.8	30.8	
Mood disorder	23.1	38.5	
Anxiety disorder	33.3	23.1	
No psychiatric diagnosis	30.8	7.7	
CGI (%)			1.00[a]
≤ Moderately ill	23.1	23.1	
≥ Moderately ill	76.9	76.9	
EEAG (range, 0-100) (Average score -*SD*-)	67.1 (*15.1*)	63.1 (*17.0*)	.444[b]
Duration of illness (Average in years -*SD*-)	14.9 (*10.3*)	14.2 (*11.5*)	.734[b]
Psychiatric hospitalisations (Average in units -*SD*-)	1.1(*2.4*)	1.1 (*1.9*)	.981[b]
Inpatient in therapeutic communities (Average in units -*SD*-)	0.47 (*0.9*)	0.23 (*0.4*)	.571[b]
MEC (range, 0-30) (Average score -*SD*-)	28.5 (*1.6*)	29.5 (*0.8*)	.047[b]
Group (%)			.593[c]
Alcohol	23.1	23.1	
THC	15.4	38.5	
Cocaine	25.6		
Alcohol + another	35.9	38.5	
MacCAT-CR (Average score -*SD*-)			
Understanding score (range, 0-26)	20.9 *(4.2)*	19 *(5.0)*	.840[b]
Appreciation score (range, 0-6)	5.1 *(1.3)*	5.1 *(0.7)*	.549[b]
Reasoning score (range, 0-8)	6.3 *(1.5)*	5.9 *(1.9)*	.178[b]
Ability to express a choice (%)			.672[c]
2	92.3	84.6	
1	5.1	15.4	
0	2. 6		
Capacity (%)			.735[c]
Yes	69.2	61.5	
No	30.8	38.5	

Note. SD: standard deviation; CGI: Clinical Global Impression Scale; EEAG: Global Assessment Scale; THC: Tetrahydrocannabinol; MEC: Mini-Mental State Examination; MacCAT-CR, MacArthur Competence Assessment Tool for Clinical Research. [a] Pearson χ 2. [b] Mann-Whitney U. [c] Fisher's statistic

Table 3. *Motivations for participating or not in research*

	Control	SUD	p
Reasons to accept participation (%)			
Altruism/desire to contribute toward scientific progress	59 (*n* = 23)	59 (*n* = 23)	1.00 [a]
Expectation of personal gain	46.2 (*n* = 18)	53.8 (*n* = 21)	.497 [a]
Desire to help others	48.7 (*n* = 19)	43.6 (*n* = 17)	.650 [a]
Other reasons, different from the above	20.5 (*n* = 8)	17.9 (*n* = 7)	.774 [a]
Reasons to reject participation (%)			
Aversion to the study	90.9 (*n* = 10)	69.2 (*n* = 9)	.327 [b]
Uneasiness concerning side effects	36.4 (*n* = 4)	46.2 (*n* = 6)	.697 [b]
Other reasons, different from the above	9.1 (*n* = 1)	15.4 (*n* = 2)	1.00 [b]

Note. SUD: Substance Use Disorder. [a] Pearson χ 2. [b] Fisher's statistic.

Table 4. *Motivations for participating in the study according to willingness to participate and group*

	Willingness to participate	Control			SUD		
		%	OR CI 95%	p	%	OR CI 95%	p
Altruism	Participates	59	1.69 (1.23-2.31)	‹.001[a]	59	4.79 (1.14-20.21)	0.25 [a]
	Does not participate	0			23.1		
Personal gain	Participates	46.2	1.52 (1.19-1.96)	.004[b]	53.8	6.42 (1.26-32.84)	‹.001 [a]
	Does not participate	0			15.4		
Help others	Participates	48.7	9.5 (1.11-81.51)	.033 [b]	43.6	4.25 (0.83-21.78)	.099 [a]
	Does not participate	9.1			15.4		
Aversion to the study	Participates	2.6	35.46 (5.08-247.63)	‹.001[b]	5.1	10.75 (4.23-27.35)	‹.001[b]
	Does not participate	90.9			69.2		
Side effects	Participates	5.1	4.19 (1.73-10.14)	.017 [b]	5.1	6.57 (3.32-13.00)	.002[b]
	Does not participate	36.4			46.2		
Other motivation	Participates	20.5	2.58 (0.29- 23.24)	.662 [b]	17.9	1.20 (0.22- 6.69)	.832[b]
	Does not participate	9.1			15.4		

Note. CI: Confidence interval; OR: Odds Ratio; SUD: Substance Use Disorder. [a] Pearson χ 2. [b] Fisher's statistic.

participation by the SUD population was aversion to the study by 69.2% (*n* = 9) followed by uneasiness concerning side effects by 46.2% (*n* = 6). As Table 3 shows, we did not find statistically significant differences between the control and SUD groups with regard to their motivations for participating in clinical research.

Table 4 shows that it was approximately 2 times more likely for controls to participate in the study if they mentioned altruism, compared with those who did not (OR 1.69, CI 95% 1.23 - 2.31; p < .001); for the SUD population, this probability was 5 times greater (OR 4.79, CI 95% 1.14 - 20.21; p = .025). Those subjects with SUD who cited receiving better treatment were approximately 7 times more likely to participate in the study (OR 6.42, CI 95% 1.26 - 32.84; p = < .001). None mentioned the possibility of receiving monetary payment as motivation for deciding to participate.

To the contrary, those who expressed aversion to the study were more likely to refrain from participating than those who did not (OR 10.75, CI 95% 4.23-27.34; p < .001). In the control group, this probability increased 35 times (OR 35.46, CI 95% 5.08-247.63; p < .001). In the SUD group, uneasiness concerning side effects was associated with the probability 7 times greater of not participating (OR 6.57, CI 95% 3.32-13.00; p = .002).

In the univariate analysis, all of the motivations cited were significantly associated in both groups with willingness/unwillingness to participate, with the exception of the domain *"Other reasons"* and, furthermore, in the SUD group, with the domain *"Desire to help others"* (Table 4). The logistic regression model included the significantly relevant variables associated with willingness to participate in the univariate analysis and variables that were relevant for limiting participation (Table 5). Just one of the variables included in the univariate analysis remained in the multivariate model: aversion to the study (OR 14.24, IC 95 % 1.31-154.8; p = .028), which made it 14 times more likely for someone to refrain from participating in the research if citing fear.

Table 5. *Factors associated with willingness to participate in research*

Associated factors	Univariate analysis		Multivariate analysis*	
	OR IC 95%	p	OR IC 95%	p
MEC	1.94 (0.99-3.79)	.054	-	-
Computer literacy	4.25 (0.988-18.29)	.052	-	-
Altruism	4.79 (1.14-20.21)	0.25	-	-
Personal gain	6.42 (1.26-32.84)	‹ .001	-	-
Aversion to the study	10.75 8 4.23-27.34) ·	‹ .001	14.24 (1.31-154.8) ·	.029
Side effects	6.57 (3.32-13.00) ·	.002	-	-

Note. MEC: Mini-Mental State Examination; OR: Odds Ratio; CI: Confidence Interval; SUD: Substance Use Disorder. *Only those factors with values of $p < .05$ are shown. The reciprocal OR is shown when the OR ‹ 1.

The model was significant χ 2 (6, N = 52) = 29.61, p = .001), explains between 43.4-64.3% of the dependent variable, and correctly classified 90.4% of the cases and is, therefore, acceptable. The Hosmer-Lemeshow test obtained a high p value, indicating that the difference between observed and predicted variables was small, χ 2 (8, N = 52) = 8.79, p = .361.

Qualitative responses

The majority of the subjects willing to participate cited altruistic reasons: they desired to *"help" "science"* or *"doctors" or "contribute toward the development of improved medications"*. Others wanted to *"improve the well-being of people"* or *"of society"*.

The second most-frequently cited reason given by those willing to participate from both groups was the expectation of receiving better treatment. These subjects mentioned that they would participate *"for their personal gain"*, "*to feel better, because I have pain"* or *"to fix my head, because it's not working properly"*. Others wanted to know more about their headache, *"let's see if you study me and tell me why this happens to me"* or *"if more doctors examine me, then I'll learn more about what's happening to me"*. Of the 53 subjects with SUD, 13 expressed altruistic and personal reasons simultaneously.

The subjects who expressed aversion to the study cited not participating *"out of fear"*, not wanting to be *"guinea pigs, there are animals for that"* or because *"experiments are dangerous"*. Some preferred to refrain from risk, given the availability of other already-contrasted medication. Neither were they willing to take new medication: *"because I don't take pills I am not familiar with"*. Others mentioned the inconvenience of *"needing to have my blood drawn"*, or claimed their dislike of taking pills *"because of their side effects"*.

Some of those who mentioned other reasons claimed that they would participate because they trusted the interviewer: "*because you request this of me, have explained it quite clearly and are very pleasant"*. Others perceived the project as an opportunity to *"interact with others"* or *"compensate for all of my previous wrongdoing"*.

Discussion

The importance of this study arises from the fact that it's the first to specifically evaluate the motivations and willingness to participate in research by people diagnosed with SUD in our setting. The majority of the participants were willing to participate in this study, in a proportion similar to that resulting in other studies (Candilis et al., 2006). This also corresponds with the 30-40% dropout rate that is commonly estimated when calculating sample sizes in epidemiological research (Marrugat, Vila, Pavesi & Sanz, 1999). No significant differences were found between the SUD and control populations concerning their willingness to participate, nor between the different substance use subgroups.

Approximately 80% of the sample (of the 205 individuals invited to participate, rejected 25) granted their consent to participate in the study applying the MacCAT-CR interview. This proportion was lower, approximately 75%, when the hypothetical trial is proposed, with a risk exceeding the minimum, given its inclusion of blood tests and side effects. This decrease in the subjects' willingness to participate allows for verifying how the perception of risk impacts participation in research. The difference between both studies could be higher, given the subjects' awareness of lower potential risk of the hypothetical trial. Likewise, having previously granted consent to participate in our study could have increased participation in the hypothetical project.

One of the elements that has the greatest influence on participation in research is the trust subjects deposit on the persons inviting them to participate (Roberts, Warner, Anderson, Smithpeter & Rogers, 2004; Stroup et al., 2005). In the CATIE study using the MacCAT-CR interview, the most

important predictive element of willingness to participate was the participant referral centre. This result could be due to the training of the professionals involved and their previous relationship with the interviewees (Stroup et al., 2005). In our case, the doctors in charge of SUD patients informed them of the possibility of this study, something which could have contributed to increasing their participation. In the controls, neither the interviewer nor another health centre staff member was directly in charge of the patients, despite having worked rotations at their centre. Though trust in researchers was a hardly cited reason for participating in the hypothetical study, it could be a factor influencing the subjects' acceptance of the MacCAT-CR interview (Figure 1).

The decision to participate or not in the hypothetical study was related only with cognitive level and computer literacy level in SUD patients. We know of no other previous research studies on the impact of computer literacy levels for the purpose of comparing our results. These findings require further exploration in future studies. In the bibliography, the relationship between willingness to participate and cognitive level, clinical severity and decision-making capacity is unclear, with results pointing in both directions. Stanley and Stanley (1982) found no differences concerning the decision to participate or not according to clinical severity or cognitive functioning. However, Candilis (2006) found an association between the decision to participate and greater decision-making capacity in accordance with the MacCAT-CR scale, lower clinical severity and lower cognitive deterioration. Our study, which concludes that there is no relationship between clinical severity, decision-making capacity and willingness to participate, is another addition to the existing bibliography on this issue that fails to endorse that association.

Previous participation in research was neither associated with higher willingness to participate nor identified as a barrier. Consequently, subjects that have never been recruited for clinical trials could be recruited if offered suitable information. Studies with user groups (Fry, Madden, Brogan & Loff, 2006b) suggest the usefulness of explaining the potential benefits of participation to research participants, and of more actively informing them of the possible impact of the results on approaches to their pathology. Even though the ethical imperatives of informed consent and the beneficence principle consider this (Beauchamp & Childress, 2009), greater emphasis is required concerning its implementation (MacNeil & Fernández, 2006).

The subjects' motivations to justify their decision to participate or not in the proposed project were coherent with the bibliography (Barrat et al., 2007; Candilis et al., 2006; Roberts et al., 2002). The arguments reasoned in favour and against were suitable, and a logical deduction of the study, for the clinical and control populations alike. Altruism as the main motivation for participating, expressed as a contribution toward science, appears in prior studies using the general population and different groups (Barrat et al., 2007; Candilis et al., 2006; Tromp et al., 2016).

The second reason for participating was the possibility of obtaining personal gain. The responses given here are related to expectations of obtaining better treatment and of gaining more knowledge about one's illness, as expressed in other studies (Candilis et al., 2006; Roberts et al., 2004). Elements associated with therapeutic error also became evident, when the expectation of obtaining a benefit shifts from being perceived as a possibility to being expressed as a conviction. This element is especially important when evaluating decision-making capacity, and is included in the MacCAT-CR interview questions. The split between reasonable therapeutic optimism and the erroneous conviction that participation entails personal well-being is governed by the level of certainty (Jansen, 2006) which is evaluated in a way similar to the assessment of thought content disorders. Therapeutic error appears as an important element in our sample, as occurred in other studies (Barrat et al., 2007; Tromp et al., 2016).

Both altruism and the possibility of personal gain were univariately associated with willingness to participate. These positive factors may be understood as potential incentives for participation in research by the SUD population, and underscore the fact that a study's real and potential benefits alike are both important for potential participants.

As also occurs in other studies, some subjects mention both motivations, altruistic and those relating to personal gain, when deciding whether or not to participate (Candilis et al., 2006). This fact reflects the complexity of properly evaluating the subjects' assessment of the research study, given its numerous determinations.

Our study did not mention economic incentives as motivation for participating in the study. This may be due to the fact that no compensation was offered for participating in the initial study, or because in our setting the idea of participating in research in exchange for money is not widespread, as is the case in other contexts (Dunn et al., 2009). Controversy exists about incentives not merely compensating for the participants' time and the inconveniences associated with participation, but that they also drive participation (Candilis et al., 2006; Misra et al., 2008). Data demonstrates the relationship between the size of the incentive and the modification of perceptions about risk and obtained benefits (Dunn et al., 2009). Research on incentives with SUD patients has attempted to establish practical guidelines for their application from an ethical perspective, respecting the principle of justice that enables distributing the research's benefits equally (Carter et al., 2012; Fry et al., 2006a).

Most participants who refused to participate expressed aversion to the study. Their responses include pejorative

language, such as being used like "guinea pigs", also frequently mentioned in the bibliography (Lebensburger et al., 2013). This factor remains in the multivariate analysis. Thus, efforts should focus on trying to overcome this limiter of participation in research.

The assessment of the risk of side effects is highly variable, and does not hinder participation if considered of minor importance, yet hinders participation when given greater importance. According to legislation currently in effect (Royal Decree 1090/2015, 2015), a research project is considered ethically acceptable if the risk/benefit ratio for the participant is adequate. Nevertheless, even in this situation, the assessment of risk differs according to a subject's personal and cultural experiences and even depends on economic incentives. However, better information could increase the similarity between perceived and real risk (Mullin, 2002) and evaluating the understanding and perception of risks could contribute toward truly validating consent. Considering these factors would allow for effectively implementing strategies to improve recruitment and adherence to clinical studies with the SUD population.

Limitations

We must consider some limitations when interpreting our results. First, our study was implemented in an urban setting with a limited number of outpatients. Further studies are necessary to evaluate our results in other settings and with different participants. A larger sample size would also allow for performing a multiple regression analysis with more variables.

Another limitation is the fact that our non-random sample and absence of other substances (like heroine and anxiolytics/hypnotics) pose concerns regarding the generalization of our results. Future studies should consider these aspects.

Given the fact that the subjects were considering a hypothetical drug for a pathology different from their own, it would be important to replicate these findings with drugs related to their illness.

Conclusions

In this study, willingness to participate of the SUD and control populations was similar. Higher cognitive level and computer literacy were more frequent among those willing to participate. Regardless of their decision to participate or not, the reasons given were adequate and coherent with literature, though elements associated with therapeutic error were also observed in both groups. Therefore, negative views about the motivations of SUD patients as research participants are unfounded. Efforts should focus on the predictive factors of willingness to participate that we have identified for the purpose of improving recruitment.

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Conflict of interests

The authors declare the inexistence of conflicts of interest.

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