Is the Mini-Mental State Examination (MMSE) useful for eligibility screening of research participants with substance use disorder?

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RESUMEN

Introducción: el Mini Examen del Estado Mental (MMSE) está recomendado para tamizaje de elegibilidad de potenciales participantes con diagnóstico de trastorno por uso de sustancias (TUS) en protocolos de investigación, debido a que las habilidades necesarias para proveer consentimiento informado válido o información precisa pueden estar deterioradas por el abuso crónico de sustancias y la presencia de algunos trastornos psiquiátricos. Hay poco conocimiento sobre la utilidad del MMSE para evaluar la alteración de estas habilidades o cuando menos sobre su capacidad de registrar efecto de TUS sobre su resultado principal. Esto tiene importantes implicaciones éticas y metodológicas. **Objetivo:** analizar los efectos del TUS, las principales sustancias de abuso, la edad de inicio de consumo, el consumo reciente y la comorbilidad psiquiátrica sobre el MMSE. El propósito final fue evaluar la utilidad del MMSE en el tamizaje de potenciales participantes de investigación. **Método:** los participantes fueron reclutados en centros de tratamiento para consumo de sustancias. Se administró cuestionario demográfico, MMSE y Mini Entrevista Neuropsiquiátrica Internacional. **Resultados:** se analizaron 601 casos para objetivo principal. Controlando grado de educación, no se encontraron efectos de edad de inicio de consumo ni de consumo reciente de sustancias específicas sobre puntaje del MMSE, según regresión lineal. Tampoco se hallaron diferencias en desempeño en MMSE con relación a las sustancias principales de abuso ($F=1.25[4,529]$, $p=.28$) ni al comparar TUS con y sin comorbilidad psiquiátrica ($F=.58[1,597]$, $p=.44$). **Discusión y conclusiones:** si de hecho existe deterioro cognitivo en esta población clínica, éste no es evaluado de forma pertinente por el MMSE. Esto arroja dudas sobre su utilidad en el tamizaje de elegibilidad.

Palabras clave: alteraciones cognitivas, comorbilidad, problemas éticos, procedimientos, reclutamiento de sujetos de investigación, trastorno por uso de sustancias.

SUMMARY

Introduction: the MMSE is used for eligibility screening of potential research participants diagnosed with substance use disorder (SUD), as abilities needed to provide a valid informed consent or accurate information could be impaired in these clinical populations. Knowledge about the capacity of the MMSE to detect impairment in these abilities or at least to assess impact of SUD on its total score, however, is rather diffuse. This has important ethical and methodological implications. **Objective:** to analyze effects of SUD only, main substances of abuse, age of onset of substance use, recent substance use, and psychiatric comorbidity upon MMSE outcome. The overall purpose of the study was to assess the utility of the MMSE for eligibility screening of potential research participants with SUD. **Method:** individuals were recruited from residential facilities for substance use treatment. A demographic questionnaire, MMSE and Mini International Neuropsychiatric Interview were used. **Results:** A total of 601 participants were gathered for main analysis. Controlling for education, no differences in MMSE score were detected within main substances of abuse ($F=1.25[4,529]$, $p=.28$), nor between SUD only versus SUD with psychiatric comorbidity ($F=.58[1,597]$, $p=.44$). Effects of age of onset and recent use of specific substances upon MMSE score were also absent. **Discussion and conclusions:** If there is some cognitive impairment in this clinical population, it may not be pertinently assessed by the MMSE, thus casting doubt on its pertinence for eligibility screening.

Key words: cognitive impairment, comorbidity, ethical issues, Mini-Mental State Examination, procedures, research subject recruitment, substance use disorder.

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INTRODUCTION

Impaired cognitive functioning can underlay or be a consequence of substance use disorder (SUD). Impairments of cognitive abilities such as working memory, decision-making, and self-awareness are often reported within studies on SUD (Goldstein & Volkow, 2011; Verdejo-García & Pérez-García, 2008; Yücel, Lubman, Solowij, & Brewer, 2007) and some psychiatric disorders (Bearden & Freimer, 2006; Robbins, Gillan, Smith, de Wi, & Ersche, 2012). This is an ethical and methodological concern in research settings, as cognitively-impaired potential research participants may have difficulties providing meaningful informed consent or accurate information (Smith, Horton, Saitz, & Samet, 2006), which in turn could have important implications, like denial of benefits of participation due to exclusion (Carter & Hall, 2008), or inaccurate data (Smith et al., 2006).

The MMSE has been recommended as a cognitive screening tool in research eligibility procedures (Smith et al., 2006). Recent clinical trials (Saitz et al., 2013; Saitz et al., 2007), cohort (Williams et al., 2007), and cross-sectional (Conner et al., 2012) studies on SUD have used the MMSE to screen for participants with sufficient capacity to consent –sometimes complemented with interviewer's judgement–, often resulting in exclusion of a considerable number of participants (e.g. a clinical trial [Saitz et al., 2013] reported 389 excluded participants from a sample of 2029, and a cohort [Saitz et al., 2007] reported 86 out of 986).

Inconsistent findings about the MMSE score's ability to predict completion of follow-up (Smith et al., 2006), values of good specificity/poor sensitivity to determine decision-making capacity in elderlies (Pachet, Astner, & Brown, 2010), and moderate associations with some proposed measures of capacity to consent in non-substance users (Palmer & Savla, 2007), might justify to an extent the use of MMSE in eligibility procedures. Nonetheless, effects of SUD upon MMSE score have not been sufficiently reported as to conclude its pertinence for eligibility screening in this context, let alone its validity to assess impact on actual abilities needed to provide meaningful consent or accurate information.

Analyzing performance of individual diagnosed with SUD on the MMSE may be a first step to ponder this pertinence, as poor execution in most of MMSE components is unlikely to occur in this pathological condition, mainly due to minimal content coverage, to ceiling effect of its items, and to the fact that, with the exception of very long-term substance abuse, SUD (especially in young individuals [American Psychiatric Association,

2013]) is not commonly associated with severe impairment of various cognitive domains assessed by the MMSE, such as speech, written and verbal comprehension, drawing, and writing (though attention and memory domains are particularly vulnerable to chronic substance use [Yücel et al., 2007], and have an important contribution to variance in MMSE final outcome [Tombaugh & McIntyre, 1992]).

The overall goal of this study was to evaluate pertinence of the MMSE for eligibility screening of potential research participants, by testing if its outcome is capable of registering SUD effects, main substances of abuse, age of onset of substance use, recent substance use, and psychiatric comorbidity.

METHOD

Study design

The current report is a secondary from a major cross-sectional multisite study (Marín-Navarrete et al., in press) aimed to validate several clinimetric scales for assessment of substance users in residential treatment in Mexico. Data was obtained from study's phases preceding administration of clinimetric scales; these phases were: 1) examination of participants' eligibility, and 2) exploration of psychiatric conditions.

Participants

The study comprised individuals from 30 residential facilities for substance use treatment in five Mexican states. Eligibility criteria were: age 18-65 (this range was established to reduce effect of cognitive decline associated to age), time in residential facility $\geq$ one week (no time limit of residency was considered), literacy, signed informed consent, and positive diagnosis for SUD (alcohol/drug dependence or abuse).

Measures

The Mexican-validated MMSE is composed by eleven domains assessing for orientation to time (5 points) and space (5 points), memory-registration (3 points), attention-calculation (5 points), memory-recall (3 points), naming (2 points), repetition (1 point), verbal comprehension (3 points), written comprehension (1 point), writing (1 point), and drawing (1 point). 30 points is the maximum score. A cutoff point ≤ 23 identifies cognitive impairment (Beaman et al., 2004). Considering influence of low educational degree, some authors (Smith et al.,

2006) have suggested a total score ≤ 20 for eligibility of research participants.

For diagnosis of SUD and other psychiatric disorders, the Mini International Neuropsychiatric Interview-5th version (MINI-5) was utilized (Sheehan et al., 1998). The following comorbidities were considered: current psychosis, current mania/hypomania, current and recurrent depressive disorder, anxiety disorders (general anxiety disorder and post-traumatic stress disorder), attention deficit/hyperactivity disorder, and antisocial personality disorder. Due to lack of exclusiveness between disorders (e.g. individuals with depression might also qualify for one or two more disorders), the evaluated psychiatric comorbidities were conceptually considered as a single variable, and thus grouped as "SUD with psychiatric comorbidity", in contrast with "SUD only" for the purpose of analysis.

Variables of substance abuse included: 1) age of onset of substance use (AOSU), through the question: "At what age did you start using [alcohol, marijuana, inhalants, cocaine and/or other substances]?"; 2) substance use before admission in treatment facility (SUBA), as a measure of recent use, through the question: "How many of the 30 days before admission to treatment did you use [alcohol, marijuana, inhalants, cocaine, and/or other substances]?"; and 3) current main substance of abuse (MSA), through the question: "What substance has caused more problems to you, or what is the substance for which you are currently under treatment?"

From a brief demographic questionnaire, the following variables were considered: gender, age, and years of education.

Procedure

All individuals were recruited for participation at each facility, after a group session with all residents to inform about the objectives and procedures of the study. MMSE and MINI-5 were administered after written informed consent and demographic questionnaire. All assessment procedures were conducted and scored by mental health professionals (e. g. psychologists) rigorously trained in the procedures of the study. All procedures were in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz.

Analyses

Frequencies and percentages of demographics were described, and between-group differences in MMSE

scores were examined through t test or one-way ANOVA for each variable. ANCOVA was conducted to evaluate differences in MMSE score within the following covariates: MSA, and SUD only/SUD with psychiatric comorbidity. Linear regression was conducted to test effects of AOSU and SUBA of specific substances on MMSE score, controlling for confounders. Confounders were selected based on significant effects on MMSE score in the demographics analysis. Differences were examined through p values and, when applicable, effect sizes (Cohen d , or η_p^2), considering $p < .05$, $d \geq .2$, $\eta_p^2 \geq .10$ as meaningful data. Cases were excluded from analysis when missing values were found. SPSS 19.0 was utilized to conduct statistical procedures.

RESULTS

650 participants completed the evaluation. 49 of them did not qualify for SUD, and did not prove any difference in MMSE score when compared to participants with SUD ($t = -.938[59.71]$, $p = .35$). Individuals without SUD were excluded from the rest of the analysis.

22 participants (3.5%) classified for impaired cognition based on MMSE score ≤ 23 , and only four (.7%) using a score ≤ 20 . Mean age was 30.28 ($SD = 10.98$); three groups were formed from the whole range of this variable, at intervals of around 16 years to facilitate reading within table 1. Comparison of MMSE score within gender and age subgroups rendered no significant differences, but did show meaningful effects of education degree on the dependent variable (see Table 1). 560 participants reported polysubstance use (at least two of the more prevalent substances [alcohol, cocaine, inhalants, and marijuana]) 30 days prior to admission to residential facility, with no significant difference observed when compared to mono-users in relation to MMSE score ($t[45.02] = .183$, $p = .85$).

Results of ANCOVA between more prevalent MSA, and between groups for SUD only versus SUD with psychiatric comorbidity, showed no meaningful effects upon MMSE score, controlling for education degree (see Table 1).

Descriptive values for AOSU and SUBA of the more prevalent substances were, respectively: alcohol ($n = 579$): $M = 17.48$ ($SD = 6.33$), $M = 9.91$ ($SD = 10.46$); cocaine ($n = 458$): $M = 19.59$ ($SD = 5.65$), $M = 7.16$ ($SD = 12.51$); inhalants ($n = 297$): $M = 17.12$ ($SD = 5.43$), $M = 7.51$, ($SD = 11.13$); and marijuana ($n = 474$): $M = 16.65$ ($SD = 4.72$), $M = 13.66$ ($SD = 37.83$). Linear regression delivered no significant effects of SUBA and AOSU upon MMSE score (see Table 2).

Table 1

MMSE score and relation with demographic variables, MSA, and SUD only/SUD with psychiatric comorbidity

Variables	n (%)	MMSE M(SD)	Statistical difference	p	Effect size
Gender			t=1.23(68.52)	.22	d = -.198
Male	540(89.9)	27.61(2.00) ^a			
Female	61(10.1)	27.20(2.56)			
Age			F=.272(2,598)	.76	$\eta_p^2 = .001$
18 to 35	436(72.5)	27.59(2.05) ^a			
36 to 55	147(24.5)	27.56(2.11)			
56 to 65	18(3.0)	27.22(2.23)			
Education degree			F=16.99(3,597)	.00	$\eta_p^2 = .079$
No completed degree	22(3.7)	24.91(3.17)			
Elementary /Secondary	363(60.4)	27.47(2.06)			
High school/College	211(35.1)	27.99(1.70) ^a			
Beyond college	5(.8)	28.60(.89)			
MSA ^b			1.25(4,529) ^c	.28	$\eta_p^2 = .009$
Alcohol	271(45.1)	27.72(1.95)			
Cocaine	124(20.6)	27.67(1.81) ^a			
Inhalants	62(10.3)	26.95(2.44)			
Marijuana	76(12.6)	27.39(2.36)			
Others ^d	66(11.0)	27.62(2.18)			
SUD only	236(39.3)	27.69(1.91)	.58(1,597) ^c	.44	$\eta_p^2 = .001$
SUD w/psychiatric comorbidity	364(60.6)	27.49(2.17)			

^a 1 missing value. ^b 2 missing values. ^c Controlling for education degree. ^d Methamphetamines, heroine, methadone, hallucinogens, sedatives and nicotine (this group was excluded from ANCOVA due to heterogeneity)

Abbreviations: MMSE=Mini-Mental State Examination; SUD=substance use disorder; MSA=main substance of abuse

Table 2

Effects of AOSU and SUBA of more prevalent substances on MMSE total score, controlling for education degree

Variable	β	CI 95%	SE	p
AOSU				
Alcohol (n = 579)	-.013	-.038 - .013	.013	.327
Cocaine (n = 458)	-.017	-.051 - .016	.017	.317
Inhalants (n = 297)	.019	-.030 - .067	.025	.451
Marijuana (n = 474)	-.001	-.041 - .038	.020	.956
SUBA ^a				
Alcohol (n = 579)	-.002	-.018 - .013	.008	.767
Cocaine (n = 458)	.004	-.011 - .019	.008	.591
Inhalants (n = 297)	-.013	-.036 - .009	.012	.251
Marijuana (n = 474)	.002	-.002 - .007	.002	.319

^a Within 30 days prior to admission in residential treatment facility

Abbreviations: AOSU=age of onset of substance use; SUBA=substance use before admission; MMSE=Mini-Mental State Examination

DISCUSSION AND CONCLUSIONS

Meaningful SUD effects (with and without psychiatric comorbidity) on MMSE score were absent, and the more prevalent MSA (alcohol, cocaine, marijuana, and inhalants), AOSU and SUBA did not prove to have a meaningful impact on performance. Only 3.5% of the analyzed sample qualified for cognitive impairment when considering a MMSE cutoff score ≤ 23 , in contrast with prevalences ranging from 8.7% to 19.1% reported for ampler samples (Saitz et al., 2007; Williams et al., 2010). When considering a score ≤ 20 (which has been advocated as more suitable for samples with low degree of education [Smith et al., 2006]), this prevalence decreased to less than 1%. This suggests that education degree, and not any substance-induced brain impairment, most likely conditioned participants' exclusion from research due to "cognitive impairment". Similar findings regarding the strong effect of education over MMSE score have been reported for clinical and normal samples (Tombaugh & MacIntyre, 1992).

Important limitations regarding variables of substance use must be stated: 1) the almost absolute polysubstance use among these participants most likely blurred the effects of specific substances; 2) absence of an eligibility criterion regarding a time limit of participants' residence at treatment facility probably conditioned findings, as the majority of participants could have resided any number of days lesser than three months (which is the more common duration of treatment in these facilities), and thus might have had different periods of abstinence and recovery; 3) neither AOSU nor SUBA referred to current MSA in all cases, as many participants reported early and recent use of more than one substance but identified only one as MSA at the time of the evaluation. These limitations, however, are not uncommon within field studies on substance use, and do not necessarily restrict findings concerning relation between broad independent variables (e.g. SUD only/with psychiatric comorbidity, or MSA) and MMSE outcome.

Results suggest that, if there is indeed some degree of cognitive impairment in subjects with SUD that could hamper potential research participation, this may not be pertinently assessed by the MMSE. Common impairments within SUD, such as deficits in working memory, decision-making, and self-awareness, which could indeed compromise the capacity of potential participants to provide meaningful informed consent or accurate information, could pass unchecked by the MMSE, even when cognitive abilities such as orientation, verbal comprehension, short-term memory, writing, or visual construction are effectively unimpaired.

Rather than using the MMSE as a mere ethical requirement out of neurology and psychiatry tradition, other measures and procedures should be further tested (e.g. Montreal of Cognitive Assessment [Copersino et al., 2009], University of California-San Diego Brief Assessment of Capacity to Consent [Jeste et al., 2007], or assessment by qualified judges [Pachet et al., 2010]), aiming to find precision in the classification of ineligible participants or to have ulterior control of effects of cognitive functioning on collected data.

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CONFLICT OF INTERESTS

The authors have no conflict of interest to declare regarding this study or the presented results.

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