

Effect of executive functioning, decision-making and self-reported impulsivity on the treatment outcome of pathologic gambling

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Background: Impairments in self-regulatory behaviour reflect a deficit in executive functioning and decision-making, as well as higher levels of self-reported impulsivity, and may be involved in the development and maintenance of addictive disorders. We sought to explore the association between self-reported impulsivity and neurocognitive measures, and their association with treatment outcome in pathologic gambling. **Methods:** We assessed patients with pathologic gambling using executive functioning and decision-making tests and self-report measures of impulsivity. Patients underwent cognitive-behavioural therapy (CBT) for pathologic gambling. **Results:** We included 88 patients (8% women) in our study. High self-reported extravagance was associated with poor performance in the Iowa Gambling Task (IGT)-ABCD version. High impulsiveness, low disorderliness, high exploratory excitability (trend), poor backward block span and poor IGT-EFGH scores (trend) predicted dropout. We observed no self-reported or neurocognitive predictors of relapse or number of treatment sessions attended. **Limitations:** Most participants were slot-machine gamblers seeking treatment. No follow-up data and no control group were included in the study. The missing sample (i.e., individuals who were recruited and assessed in the pretreatment stage but who chose not to begin treatment) had higher extravagance scores than the final sample. **Conclusion:** Neurocognitive reward sensitivity was related to self-reported overspending behaviour. Self-regulatory impairments (especially rash impulsiveness and punishment sensitivity) and executive dysfunction predicted only dropout of CBT in participants with pathologic gambling. Different neurocognitive processes and personality traits might mediate treatment response to psychological therapy of pathologic gambling according to the specific target variable assessed.

Introduction

Impairments in self-regulatory behaviour seem to be involved in the development and maintenance of pathologic gambling and other addictive disorders.^{1,2} From a neuropsychological point of view, this impairment reflects a deficit in executive functioning and decision-making.^{3,4}

Executive functioning includes functions such as cognitive flexibility (set-shifting), which is associated with orbitofrontal functioning, and working memory, planning and abstract thinking, which are associated with dorsolateral prefrontal functioning.⁵⁻⁷ However, decision-making seems to be mainly associated with activation of the ventromedial prefrontal cortex.^{5,8} People with pathologic gambling have shown impaired

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performance in tasks measuring both concepts. Specifically, studies report deficits in cognitive inhibition, complex executive functions and attention.⁹⁻¹¹ This population also shows impairments in decision-making.¹²⁻¹⁴ Decision-making impairments are observed in impulsive individuals in general. Specifically, impulsive individuals show an insensitivity to variations in reward/loss magnitude of behavioural decision-making tasks.^{15,16} Sensitivity to reward has been the most studied aspect of decision-making. However, decision-making is also guided by sensitivity to punishment,¹⁷ which has received little attention in pathologic gambling, especially from a neurocognitive perspective.

Self-regulatory deficits may also manifest in certain personality traits such as impulsivity. Considering its multidimensionality, at least 2 types of impulsivity have been postulated: rash impulsiveness (acting rashly when distressed) and sensitivity to reward (greater response/activation to rewarding stimuli). The latter is based on Gray's Behavioural Approach System.¹⁸ In the field of substance dependence, some authors consider rash impulsiveness to be a risk factor for uninhibited behaviour and for the progression from substance use to substance dependence, whereas sensitivity to reward is considered to be associated more with motivation to use substances than with substance dependence.^{19,20} However, there is confusion regarding some impulsivity-related terms that are not clearly classified into the previous 2-factor hypothesis. For instance, sensation-seeking (similar to novelty-seeking), which has been defined as a need for varied, novel and stimulating experiences,²¹ has been associated with heightened sensitivity to the rewarding effects of drugs.^{22,23} Sensation-seeking has also been associated with reward-seeking in animal studies,²⁴ and it seems to be independent of rash impulsiveness.²⁵ However, many studies of pathologic gambling use the terms impulsiveness and sensation-seeking indistinctly, and most of them report high levels of both traits in this population.²⁶⁻²⁸ Rash impulsiveness would represent a failure to inhibit a behaviour that may result in negative consequences, lack of reflection and planning, rapid decision-making and action and carelessness.^{29,30} Given the definition of both concepts (rash impulsiveness and sensation-seeking), sensation-seekers are not necessarily careless or nonreflective. As such, we should expect a stronger association between sensation-seeking and sensitivity to reward than sensation-seeking and rash impulsiveness.

The novelty-seeking factor of the Temperament and Character Inventory-Revised³¹ tool is considered to be a general measure of impulsivity. However, its different subscales seem to measure different components of this construct. Exploratory excitability (reflecting sensation-seeking) and extravagance (reflecting overspending behaviour and poor planning) have been related to polymorphisms in the dopamine (DA) D4 receptor (DRD4).³² These traits have been considered to represent the exploratory, extravagant and extroverted subtypes of the novelty-seeking factor. Conversely, the impulsive and monotony-avoiding subtypes would be represented by the impulsiveness (representing unreflective and careless behaviour) and the disorderliness (reflecting disorganized, uncontrolled, antinormative behav-

our) subscales.³² The literature about the relation between Cloninger's novelty-seeking subscales and the different components of impulsivity is scarce.^{33,34} Nevertheless, considering these findings in the framework of the previously mentioned 2-factor hypothesis, we may expect an association of exploratory excitability and extravagance with sensitivity to reward on the one hand, and impulsiveness and disorderliness with rash impulsiveness on the other. The distinction between these concepts and their association with self-regulatory deficits in pathologic gambling is understudied. Further, relatively few studies appear to have examined the relations between these traits and treatment outcome.

In spite of the importance of impulsivity in the generation and maintenance of pathologic gambling, the link between neuropsychological and personality (self-report) measures of impulsivity (as a whole) is relatively unexplored in the field of pathologic gambling. In addition, only 1 study has focused on the association of neuropsychological and personality measures of impulsivity with treatment outcome in pathologic gambling. Goudriaan and colleagues³⁵ examined the effect of neuropsychological functions (disinhibition, perseveration for reward, cognitive flexibility, decision-making) and self-report measures of impulsivity and sensitivity to punishment on vulnerability to relapse after psychological treatment for pathologic gambling. They found that only disinhibition and perseveration for reward (as measured by neuropsychological tasks) were predictive of relapse at 1-year follow-up after treatment. No other neuropsychological predictors were identified, and no self-report measure was predictive of relapse. They concluded that neuropsychological measures, particularly disinhibition and perseveration for reward, are more powerful predictors of treatment outcome than personality measures. In this regard, Forbush and colleagues³⁶ explored the predictive power of neuropsychological (general intellectual functioning, executive functioning, decision-making) versus personality (general personality and impulsivity) measures in a group with diagnosed pathologic gambling compared with healthy controls. They generated 2 neuropsychological factors and 2 personality factors (by factor analysis of the different measures) and used these converted variables as explanatory variables. In contrast to Goudriaan and colleagues,³⁵ Forbush and colleagues³⁶ found that personality measures were better predictors of a pathologic gambling diagnosis than neuropsychological functions. Both research groups used different outcome measures, but to our knowledge, only these 2 studies have addressed the specific role of neuropsychological and personality measures in pathologic gambling.

Differentiating the specific role of every measure may help clarify the mechanisms underlying problem gambling behaviour. Adinoff and colleagues³⁷ concluded that the different behavioural manifestations of impulsivity may correspond to different neurocognitive constructs with specific neuroanatomical correlates. Then, impulsivity should be described not only in terms of phenotypes (as measured by self-report tests) but also from an endophenotypic/neuropsychological point of view. These authors recommend the study of the relation between impulsive behaviours, neurobiological impairments and

risk of relapse in addictive disorders. Llewellyn³⁸ also highlighted the importance of exploring the relation between neuropsychological measures of risk-related decision-making and personality traits.

In sum, very little research about the link between neurocognitive (endophenotypical) and self-report (exophenotypical) measures of both impulsivity and self-regulatory deficits has been done, particularly in the area of pathologic gambling. Second, the association between these constructs and treatment outcome in pathologic gambling has received little attention. In this context, we aimed to determine the relations between self-reported impulsivity, neurocognitive functions (executive functioning and decision-making, including both reward and punishment sensitivity) and treatment outcome (including both relapse and dropout) in pathologic gambling. Our specific objectives were, first, to establish the pattern of associations between neurocognitive variables and self-report (personality) measures of impulsivity in pathologic gambling and, second, to determine the predictive power of neuropsychological and personality measures in relation to relapse and dropout during psychological treatment for pathologic gambling.

Methods

Participants

We recruited consecutive patients seeking treatment for pathologic gambling in a Pathological Gambling Unit (Department Psychiatry, University Hospital of Bellvitge, Barcelona, Spain) for participation in our study. Pathologic gambling was diagnosed according to DSM-IV-TR criteria.³⁹ Entry into the study was from November 2005 to September 2007. Exclusion criteria at intake were age younger than 18 or older than 65 years, history of neurologic disorder or head injury, psychotic disorder and history of substance abuse in the previous 3 months. Substance abuse was measured with the substance use disorders module of the Structured Clinical Interview for DSM-IV Axis I Disorders.⁴⁰ We assessed patients with the South Oaks Gambling Screen (SOGS).⁴¹

This study was carried out according to the latest version of the Declaration of Helsinki. The University Hospital of Bellvitge Ethics Committee of Clinical Research approved this study, and we obtained informed consent from all final participants.

Instruments and measures

Self-report measure of impulsivity

Novelty-seeking is 1 of 4 temperamental factors measured by the Temperament and Character Inventory-Revised (TCI-R) tool.³¹ It reflects several forms of impulsivity,³¹ and its reliability (internal consistency) was 0.77 (Cronbach's α) in the Spanish adaptation of the TCI-R.⁴² Given our interest in the different aspects of impulsivity, rather than the total score, we focused on the 4 novelty-seeking subscales: exploratory excitability (NS1), impulsiveness (NS2), extravagance (NS3) and disorderliness (NS4). The NS2, NS3 and NS4 subscales

showed low intercorrelations (all below 0.4) in our sample, and NS1 (exploratory excitability) was completely independent of the other 3 subscales.

Neurocognitive measures

The Wisconsin Card Sorting Test (WCST)⁴³ is considered to be sensitive to frontal lobe dysfunction. It measures strategic planning, organized searching, using environmental feedback to shift cognitive sets, directing behaviour toward achieving a goal and modulating impulsive responding. The materials consist of 2 decks of 64 cards that are numbered from 1 to 64 on the lower left corner of the reverse side to ensure a standard order of presentation. The participant must sort response cards to 4 key cards according to colour, form or number (categories) and alter their approach as shifts in the sorting principle occur. The examiner gives only feedback of "correct" or "incorrect" on every trial. The test finishes when the examinee completes either 6 categories or 128 trials. The WCST provides objective scores for overall success and for specific sources of difficulty in the task such as perseveration or conceptualization. For the present study, we used the number of completed categories and the percentage of perseverative and nonperseverative errors.

The Stroop Colour and Word Test⁴⁴ measures cognitive flexibility, involuntary attention, ability to override a prepotent response (reading a lexical stimulus) and concentration effectiveness.⁴⁵ It consists of a word page (first list) with colour words printed in black ink, a colour page (second list) with "Xs" printed in colour and a colour-word page (third list) with names of colors printed in an incongruent colour. The examinee must read words (first list) or name ink colour (second and third lists) as quickly as possible within a time limit (45 s). The test yields 3 scores based on the number of items correctly completed on each of the 3 stimulus sheets, i.e., number of read words in first list (W), number of colour-named items in second list (C) and number of colour-named words in third list (CW). In addition, Golden⁴⁴ proposed an interference score, which is useful in determining the individual's cognitive flexibility, creativity and reaction to cognitive pressures. This score is computed according to the following formula: $\#CW - (\#W \times \#C) \div (\#W + \#C)$. Higher scores in this index suggest better cognitive inhibition (better interference control).

The Trail Making Test, parts A and B (TMT),⁴⁶ is an easily administered test of visual conceptual and visuomotor tracking involving motor speed, attention and the ability to alternate between cognitive categories (set-shifting). This test consists of 2 parts. Part A is a page with 25 numbered circles randomly arranged. Participants are instructed to draw lines between the circles in increasing sequential order until they reach the circle labelled "end." Part B is a page with circles containing the letters A through L and 13 numbered circles intermixed and randomly arranged. Participants are instructed to connect the circles by drawing lines alternating between numbers and letters in sequential order, until they reach the circle labelled "end." If individuals make mistakes, the mistakes are quickly brought to their attention, and they continue from the last correct circle. The test takes about

5–10 minutes to complete. Scores are the amount of time taken to complete each part. To control for individual differences in motor speed, we generated a score based on the subtraction of time to complete part A from time to complete part B. Higher scores suggested set-shifting difficulties.

The Iowa Gambling Task (IGT), versions ABCD and EFGH,¹⁷ is a computerized test measuring sensitivity to reward (i.e., to what extent large immediate gain outweighs even larger future loss; ABCD version) and sensitivity to punishment (i.e., to what extent immediate punishment outweighs high reward; EFGH version). It seems that patients with ventromedial prefrontal lesions perform poorly on both versions.¹⁷ Participants receive standard instructions and are informed that the aim of the game is to win as much money as possible. In the ABCD version, 4 decks of cards are presented on the computer screen. The participant has to pick cards after which the amount of money the participant has won or lost is depicted on the computer screen. Winning or losing money is indicated by a green bar that increases or decreases. The game consists of 100 trials. The ABCD version is focused on rewards. Decks A and B are associated with great immediate reward but even greater future punishment. These are known as the disadvantageous decks. Decks C and D give lesser rewards but also lesser losses, so they result in a net gain in the long run. The layout and structure of the EFGH version is very similar. Instructions are the same, but this version is focused on punishment. Decks E and G are associated with great immediate punishment but even greater future reward. Decks F and H are associated with lesser punishments but also much lesser rewards, so they are the disadvantageous decks. Information about advantageous/disadvantageous decks is not given to the participant; they have to infer this information based on feedback. The 100 trials of each version are divided into 5 equal blocks. The final score reflects the number of cards selected from advantageous decks minus disadvantageous decks for each block (ABCD version: [C+D] – [A+B]; EFGH version: [E+G] – [F+H]). We counterbalanced the order of administration of both versions, which were also administered in different sessions.

The Controlled Oral Word Association Test⁴⁷ is also known as the FAS test of verbal fluency in reference to the letters F-A-S, which are used for word generation. Its purpose is the spontaneous production of words beginning with a given letter or of a given class within a limited amount of time (verbal association fluency). It measures the individual's ability to spontaneously produce words pertaining to a specific phonemic category. This test presumably reflects both preservation of word knowledge and ability to self-initiate verbal output⁴⁸ (i.e., executive functioning). The participant is asked to produce as many words as possible beginning with a given letter in 1 minute. Proper nouns, repetitions and variations are inadmissible. In Spanish, the letters P-M-R are used instead of F-A-S.⁴⁹ The score is the sum of all admissible words for the 3 letters.

The Backward Digits Span task⁵⁰ of the Wechsler Memory Scale, third edition, requires the examiner to verbally present digits at a rate of 1 per second. The participant is asked to repeat the list of digits after the examiner has completed

delivering it. The forward test requires the participant to repeat the digits verbatim. The backward test requires the participant to repeat the digits in reverse order. The number of digits increases by 1 until the participant consecutively fails 2 trials of the same digit span length. Performance on the backward digit span task measures verbal working memory by requiring internal manipulation of mnemonic representations of verbal information in the absence of external cues.⁵¹ Given our focus on executive functions, we used the digit span length in the backward version (backward digits span [BDS]).

The Corsi blocks task⁵² apparatus consists of a set of 9 identical blocks irregularly positioned on a plastic board. The experimenter points to a series of blocks at a rate of 1 block per second. Subsequently, the participant is required to point to the same blocks in their order of presentation (forward) or in the reversed order (backward). The length of the block sequences increases until recall is no longer correct. The Corsi blocks task involves visuospatial and executive resources by requiring backward recall of the path presentations in the task. Upon presentation of a series of block positions, a representation of the path is constructed and maintained in visuospatial working memory. If the sequence has to be reproduced in reverse order, executive control is required.⁵³ For the present study, we analyzed the blocks span in the backward version (backward blocks span [BBS]).

Treatment outcome

Dropout

Milton and colleagues⁵⁴ and Robson and Edwards⁵⁵ defined dropout as terminating treatment before completing the predetermined treatment program (see below) that was administered. This was coded as a binary variable (dropout/nondropout). We used the number of treatment sessions attended to analyze dropout from a continuous perspective.

Relapse

Ledgerwood and Petry⁵⁶ defined relapse as the presence of any episode of gambling during treatment associated with a subjective sense of loss of control over gambling. This variable was quantified for all patients who started treatment (including those who dropped out during treatment). Relapse was coded as a binary variable (relapse/nonrelapse) and continuously (number of relapses during treatment).

Procedures

We first assessed patients with a semistructured face-to-face interview as part of the usual protocol in our unit. This interview includes the assessment of substance abuse/dependence and is usually performed by psychologists or psychiatrists (minimum 10 yr of specialization in pathologic gambling). Exclusion criteria for the current study were identified at this time. The patients who agreed to participate in the study provided written, informed consent after receiving written and oral explanation of the procedures.

Patients completed the TCI-R during a second session. The

neurocognitive assessment was then administered by an experienced neuropsychologist during 2 sessions of 45 minutes' duration before starting treatment. We also administered the Wechsler Adult Intelligence Scale, third edition (WAIS-III)⁵⁷ vocabulary subtest as a measure of estimated intelligence.⁴⁵

Treatment consisted of a cognitive-behavioural outpatient group therapy (CBT) based on a standardized protocol.³⁸ It consisted of 16 weekly outpatient sessions (90 min each) with a total of 10–14 patients per group. The main objective of the treatment was training patients to put into practice CBT strategies to achieve full and definitive abstinence from gambling. Techniques used were psychoeducation on the disorder, stimulus control, response prevention, cognitive restructuring, reinforcement and self-reinforcement, skills training and relapse prevention techniques. The therapist recorded dropouts and relapses based on patients' oral reports and written diaries and relatives' confirmation.

Statistical analysis

We performed all statistical analyses with SPSS version 15.0.1 for Windows. We compared background characteristics (age, education, WAIS-III vocabulary score, duration of gambling problem and SOGS total score, sex, marital status, employment, use of medication) of patients who dropped out versus those who did not, and individuals who relapsed versus those who did not, using analysis of variance (ANOVA) for quantitative variables and the χ^2 test for qualitative variables.

The association between self-report measures of impulsivity (TCI-R novelty-seeking subscales) and neurocognitive measures of decision-making and executive functioning was assessed through linear regression models. Considering the natural direction of the relation between endophenotypes and external phenotypes, we used neurocognitive and decision-making measures as independent explanatory variables, and TCI-R novelty-seeking subscales were used as dependent variables. We generated 4 models (1 for each subscale) by entering all independent variables in 1 block. All 4 models were adjusted for age, sex and score in the WAIS-III vocabulary subtest (entered in block 2).

We measured the association between neurocognitive, decision-making and self-report measures on the one hand and treatment outcome on the other through logistic and linear regression models. We assessed 4 models: 2 logistic regression models for categorically coded dropout and relapse and 2 linear regression models for number of treatment sessions attended and number of relapses, respectively. The independent measures were entered as a block to explore the relative contribution of each predictor to treatment outcome.

Results

Patients

We assessed a total of 115 patients, but 27 (23.5%) rejected starting treatment. The final sample consisted of 88 patients with pathologic gambling (8% were women), with a mean age of 36.7 years (standard deviation [SD] 11.1 yr). The mean

score on the SOGS⁴¹ was 10.3 (SD 2.7). The patients had a mean of 10.7 (SD 3.2) years of education, 83.5% were employed, 52.9% were married, 34.1% were single and the remaining 13% were separated or divorced. Most participants (91.7%) were mainly slot-machine gamblers and 23.1% had several gambling problems, including slot machines, bingo, casino, lotteries and cards. The mean duration of the gambling problem was 5.6 (SD 5.7) years. Only 17.4% of patients were taking psychiatric medication, primarily antidepressants: 75.0% selective serotonin reuptake inhibitors (SSRIs) and 37.5% benzodiazepines.

In relation to patients who started treatment, Student *t* tests revealed that those who rejected treatment exhibited higher levels of TCI-R extravagance (NS3; $t_{90,9} = 5.0$, $p < 0.001$) and a slightly higher percentage of nonperseverative errors in the WCST ($t_{108} = 2.0$, $p = 0.048$).

The treatment outcome groups were as follows: 45 patients showed no dropout or relapse, 12 patients had a relapse, 20 patients had dropout and 7 patients showed both relapse and dropout during treatment (we missed information about relapse from 4 patients who had dropouts). Table 1 shows the main sociodemographic and clinical characteristics per group. We identified no statistically significant group differences in any of the variables presented in Table 1.

Relation between self-report measures of impulsivity and neurocognitive measures

Table 2 shows the result of bivariate correlations between self-report and neurocognitive measures. Although several correlations were significant at a 0.05 level, no statistically significant correlations were observed after Bonferroni correction, which was set up at a 0.001 level.

Regarding the association analysis, only the adjusted model for the NS3 subscale (extravagance) was statistically significant ($F_{13,67} = 2.26$, $p = 0.015$). Specifically, the IGT-ABCD net score was negatively associated with the NS3 score ($B = -0.057$, standard error = 0.026, $\beta = -0.245$, $t = -2.17$, $p = 0.033$). No other neurocognitive index was statistically associated with the NS3 score. No other model was statistically significant (NS1, $p = 0.27$; NS2, $p = 0.13$; NS4, $p = 0.37$). These results remained after excluding medicated patients from the sample.

Effect of neurocognitive and self-report measures on treatment outcome

Table 3 shows means and standard deviations of personality and neurocognitive measures according to the presence of dropout or relapse.

Dropout

The result of the logistic regression analysis for dropouts is shown in Table 4. Dropout during treatment was significantly predicted by high NS2 (impulsiveness) and low NS4 (disorderliness) scores, as well as lower number of blocks recalled at the BBS. High NS1 (exploratory excitability) and lower number of advantageous choices in the IGT-EFGH predicted dropouts at a trend level. The model was statistically

significant ($\chi^2_{14} = 34.71, p = 0.002$) and explained a moderate to high percentage of variance in dropouts (Nagelkerke $R^2 = 0.647$). No differences in these results were observed after adjustment for age and sex. The exclusion of medicated patients yielded the same pattern of effects, but the TCI-R NS4 subscale lost statistical significance ($p = 0.19$).

Regarding the linear regression analysis for number of treatment sessions attended, the model was not statistically significant ($F_{14,23} = 1.165, p = 0.36$). This result remained after excluding medicated patients from the analysis.

Relapse

The logistic regression model for relapse did not achieve statistical significance ($\chi^2_{14} = 14.21, p = 0.43$). The linear regression model for number of relapses also failed to achieve statistical significance ($F_{14,14} = 0.847, p = 0.62$). These results remained after we excluded medicated patients from the analyses.

Discussion

The present study focused on the relations between neurocognitive measures (executive functioning and decision-making), self-report measures of impulsivity and treatment outcome in pathologic gambling.

Relation between self-report measures of impulsivity and neurocognitive measures

We observed that individuals with pathologic gambling who had high levels of TCI-R novelty-seeking extravagance (i.e., unwary, overspending individuals who were outrageous in relation to money, energy and feelings) showed higher sensitivity to reward. Other authors have also found a relation between some aspects of impulsivity and sensitivity to reward, as measured by the IGT.⁵⁹⁻⁶¹ We can conclude from these

Table 1: Sociodemographic and clinical characteristics of the treatment outcome groups of patients with pathologic gambling

Characteristic	Group; mean (SD)*			
	No relapse, no dropout, n = 45	Relapse, n = 12	Dropout, n = 20	Relapse and dropout, n = 7
Age, yr	37.4 (10.8)	40.1 (12.2)	32.1 (6.7)	36.3 (14.4)
Sex, male:female	2:43	1:11	2:18	2:5
Education, yr	10.6 (2.7)	11.8 (3.3)	10.7 (4.1)	10.9 (3.7)
WAIS-III vocabulary subtest score	34.9 (8.4)	38.2 (9.8)	36.0 (7.4)	33.7 (10.0)
Marital status, %				
Single	27.9	45.5	40.0	28.6
Married	58.1	45.5	50.0	42.8
Divorced	14.0	9.0	10.0	28.6
Employed, %	83.7	90.9	85.0	85.7
Duration of pathologic gambling, yr	6.3 (6.4)	6.7 (5.2)	4.6 (5.6)	3.6 (1.7)
Medicated, %	10.5	22.2	23.1	25.0
SOGS score	9.9 (2.6)	10.5 (2.6)	9.8 (2.9)	12.4 (2.7)

*Unless otherwise indicated.
SD = standard deviation; SOGS = South Oaks Gambling Screen;⁴¹ WAIS-III = Wechsler Adult Intelligence Scale, third edition.⁶⁷

Table 2: Pearson product-moment correlations between self-report (TCI-R novelty-seeking subscales) and neurocognitive measures

TCI-R subscale	COWAT	SCWT interf.	BDS	BBS	TMT B-A difference	WCST categories	WCST % errors		IGT net score	
							Pers.	Nonpers.	ABCD	EFGH
Exploratory excitability										
r	0.020	0.013	0.002	0.206	-0.030	-0.062	-0.097	0.138	0.095	0.061
p value	0.83	0.89	0.99	0.035	0.76	0.54	0.33	0.17	0.35	0.52
Impulsiveness										
r	0.056	0.171	0.061	0.131	0.028	0.118	-0.284	0.160	0.050	0.070
p value	0.54	0.07	0.54	0.18	0.78	0.24	0.004	0.11	0.62	0.47
Extravagance										
r	0.049	0.010	0.128	-0.014	0.037	-0.226	0.165	0.272	-0.232	-0.019
p value	0.60	0.92	0.19	0.89	0.71	0.023	0.10	0.006	0.019	0.85
Disorderliness										
r	-0.048	0.152	0.003	0.099	0.047	-0.026	-0.098	0.142	-0.192	0.044
p value	0.61	0.10	0.98	0.32	0.64	0.79	0.33	0.16	0.06	0.65

BBS = Backward Blocks Span;⁶² BDS = Backward Digits Span;⁶⁰ COWAT = Controlled Oral Word Association Test;¹⁷ IGT = Iowa Gambling Task;¹⁷ Nonpers. = nonperseverative; Pers. = perseverative; SCWT interf. = Stroop Colours and Words Test Interference;⁴⁴ TCI-R = Temperament and Character Inventory-Revised;^{31,42} TMT = Trail Making Test;⁴⁶ WCST % errors = Wisconsin Card Sorting Test⁴³ % of errors.

studies that particularly poor planning is associated with high sensitivity to reward. High scores in the TCI-R novelty-seeking extravagance subscale indicate lack of both caution and farsighted behaviour, which can be related to poor planning abilities. Our results add support to the literature in this regard. We can hypothesize that the extravagance subscale is the most related to cognitive impulsivity or reward-discounting (i.e., the preference for smaller, immediate rewards over larger, delayed rewards), which is associated with IGT-ABCD performance.⁶² High scores in the TCI-R novelty-seeking extravagance subscale have also been related

to low baseline cerebral availability of the type 1 cannabinoid receptor (CB1R) in healthy volunteers,⁶³ hypercortisolemia in depressed patients⁶⁴ and a higher level of tobacco dependence.⁶⁵

Unlike other studies,^{16,66} we found no association between other aspects of self-reported impulsivity, such as novelty-seeking impulsiveness and exploratory excitability, and neurocognitive measures. We must take into account that the studies measuring the association between impulsivity (as a whole) and neurocognition use different samples and instruments to assess these concepts, so the comparison across studies may be difficult. In fact, we know of no studies

Table 3: Personality (TCI-R novelty-seeking subscales) and neurocognitive measures according to dropout and relapse

Measure	Outcome; mean (SD)			
	Dropout		Relapse	
	No, n = 57	Yes, n = 31	No, n = 65	Yes, n = 19
TCI-R subscale				
Exploratory excitability	29.1 (4.7)	29.7 (5.1)	29.6 (4.8)	28.9 (4.8)
Impulsiveness	24.5 (4.7)	26.3 (5.0)	24.4 (4.8)	27.9 (4.3)
Extravagance	31.0 (6.0)	33.5 (6.5)	31.3 (6.2)	33.5 (6.7)
Disorderliness	20.8 (4.9)	20.1 (4.2)	20.2 (4.9)	21.2 (3.7)
COWAT	40.9 (13.3)	35.8 (10.4)	39.6 (12.0)	38.9 (14.8)
SCWT interference	-0.3 (11.2)	-1.5 (11.6)	-1.3 (11.2)	0.3 (10.3)
BDS	6.5 (2.3)	5.7 (1.8)	6.4 (2.2)	6.0 (2.1)
BBS	7.5 (1.8)	6.5 (2.2)	7.5 (1.8)	6.8 (2.1)
TMT B-A difference	48.7 (43.8)	66.5 (51.3)	51.5 (43.8)	53.6 (43.7)
WCST categories	4.1 (2.0)	4.7 (1.6)	4.3 (1.9)	4.5 (1.9)
WCST % perseverative errors	21.1 (14.3)	18.5 (10.8)	20.4 (13.8)	17.5 (10.1)
WCST % nonperseverative errors	14.2 (8.1)	14.3 (7.5)	13.9 (7.8)	15.5 (8.1)
IGT-ABCD net score	3.1 (22.9)	-4.2 (28.7)	1.8 (24.7)	-2.1 (27.2)
IGT-EFGH net score	6.0 (26.7)	0.6 (24.8)	4.5 (28.6)	5.2 (19.6)

BBS = Backward Blocks Span;⁶² BDS = Backward Digits Span;⁵⁰ COWAT = Controlled Oral Word Association Test;⁴⁷ IGT = Iowa Gambling Task;¹⁷ SCWT = Stroop Colours and Words Test;⁴⁴ TCI-R = Temperament and Character Inventory-Revised;^{31,42} TMT = Trail Making Test;⁴⁶ WCST = Wisconsin Card Sorting Test.⁴³

Table 4: Logistic regression analysis for dropouts (enter method)

Measure	B	Standard error	Wald	Degrees of freedom	p value	OR (95% CI)
TCI-R subscale						
Exploratory excitability	0.293	0.172	2.905	1	0.09	1.341 (0.957-1.879)
Impulsiveness	0.346	0.171	4.089	1	0.043	1.413 (1.011-1.977)
Extravagance	-0.010	0.092	0.012	1	0.91	0.990 (0.827-1.185)
Disorderliness	-0.375	0.161	5.432	1	0.020	0.688 (0.502-0.942)
COWAT	0.943	0.679	1.929	1	0.16	2.569 (0.678-9.726)
SCWT interference	-0.081	0.100	0.661	1	0.42	0.922 (0.758-1.121)
BDS	0.025	0.109	0.052	1	0.82	1.025 (0.828-1.270)
BBS	-0.057	0.048	1.383	1	0.24	0.945 (0.860-1.039)
TMT B-A difference	0.032	0.054	0.342	1	0.56	1.032 (0.929-1.147)
WCST categories	< 0.001	0.012	0.001	1	0.97	1.000 (0.977-1.025)
WCST % pers. errors	-0.453	0.343	1.744	1	0.19	0.636 (0.325-1.245)
WCST % nonpers. errors	-0.615	0.304	4.084	1	0.043	0.541 (0.298-0.982)
IGT-ABCD net score	-0.025	0.020	1.549	1	0.21	0.976 (0.939-1.014)
IGT-EFGH net score	-0.039	0.021	3.499	1	0.06	0.962 (0.924-1.002)
Constant	-4.627	8.022	0.333	1	0.56	0.010 —

BBS = Backward Blocks Span;⁶² BDS = Backward Digits Span;⁵⁰ CI = confidence interval; COWAT = Controlled Oral Word Association Test;⁴⁷ IGT = Iowa Gambling Task;¹⁷ nonpers. = nonperseverative; OR = odds ratio; pers. = perseverative; SCWT = Stroop Colours and Words Test;⁴⁴ TCI-R = Temperament and Character Inventory-Revised;^{31,42} TMT = Trail Making Test;⁴⁶ WCST = Wisconsin Card Sorting Test.⁴³

assessing the relation between the TCI-R novelty-seeking subscales and neurocognitive function. Even so, other investigations have also failed to find associations between sensation-seeking (represented by exploratory excitability in the present study) and decision-making in other samples with addictive behaviours such as cigarette smokers⁶⁷ or undergraduate students.⁵⁹ In the same line, Zermatten and colleagues⁵⁹ assessed the relation between the UPPS Impulsive Behaviour Scale⁶⁸ (measuring urgency, premeditation, perseverance and sensation-seeking) and the IGT-ABCD in undergraduate students, and they only found an association between lack of premeditation (which would be close to the novelty-seeking extravagance subscale) and poor decision-making.

Effect of neurocognitive and self-report measures on treatment outcome

Relapse

In contrast to the study by Goudriaan and colleagues,³⁵ who found that neurocognitive measures, more than self-report measures, were the most predictive of relapse in pathologic gambling, no self-report measure of impulsivity or neurocognitive measures were predictive of relapse (both from a categorical or a continuous approach) in the present study. This finding suggests that self-reported impulsivity, executive functioning and decision-making do not mediate relapse during treatment in pathologic gambling, so other factors, such as other personality traits, psychopathological status and motivation at the beginning and during treatment, should be explored.

In addition, contrary to what should be expected, some statistically nonsignificant trends (Table 3) suggested that those who relapsed during treatment tended to have better cognitive inhibition and lower perseverative tendencies. This means that relapse during treatment could not be attributed to poor neurocognitive performance. These are preliminary and nonsignificant results that need corroboration in future studies.

The lack of agreement between the present results and those of Goudriaan and colleagues may reflect the use of different self-report measures in both studies, as well as the fact that Goudriaan and colleagues measured relapse at 1-year follow-up, whereas in the present study this measure was taken during treatment. This might suggest that the processes controlling vulnerability to relapse are different during treatment and follow-up. Whereas risk of relapse would not be related to self-reported impulsivity or neurocognitive function during treatment, the long-term maintenance of abstinence would require the intervention of neurocognitive/endophenotypical markers, such as perseveration for reward and disinhibition.

Finally, we should consider that sample-specific factors such as a small sample size or the main presence of slot-machine gamblers may have masked the present results.

Dropout

We found that dropout during treatment (from a categorical point of view) was predicted by both self-report measures and neurocognitive variables. High TCI-R impulsiveness was pre-

dictive of dropouts. High TCI-R exploratory excitability also predicted dropout at a trend level. These results suggest that especially rash impulsiveness and, to a lesser degree, sensation-seeking are involved in risk for dropout in pathologic gambling, whereas no impulsivity trait has an influence on relapse. In addition, low TCI-R disorderliness (i.e., strict regimentation, organization, rigidity and overcontrol), which correlates negatively with impulsivity, also predicted dropout. The latter finding may be related to an excessive sense of guilty (frequently described in pathologic gambling⁶⁹) or false beliefs about treatment or the therapist that yield emotions, including apathy, discouragement and shame, that finally lead patients with pathologic gambling to drop out of treatment.⁷⁰ From another point of view, Vassileva and colleagues⁶¹ observed that high scores in antisocial personality were associated with better IGT-ABCD performance (reflecting sensitivity to reward from a neurocognitive perspective) in substance-dependent individuals, suggesting that this trait was related to better cognitive impulse control. High TCI-R disorderliness scores are associated with antisocial traits, which in the present study (similar to the study by Vassileva and colleagues⁶¹) were associated with lower risk of dropout. Along these lines, Gullo and Dawe⁷¹ stated that impulsivity also has positive aspects (see Dickman⁷² and Caci and colleagues⁷³ for the concept of functional v. dysfunctional impulsivity). However, we must take into account that the relation between low disorderliness and dropout in the present study lost statistical significance after we excluded medicated patients from the sample, so the association between this trait and dropout might be circumscribed to special characteristics of patients taking medication.

Moreover, poor spatial working memory (suggestive of executive dysfunction) was associated with greater risk of dropout. Working memory deficits have also been reported in people with gambling problems.⁷⁴ The present results suggest that this deficit may confer higher risk for dropout among those who seek treatment.

Poor IGT-EFGH performance was also associated with higher risk of dropout at a trend level, suggesting that those individuals who drop out of treatment tend to show an increased sensitivity to punishment and, in turn, an insensitivity to the future consequences of their actions/decisions.^{3,17} This finding suggests that individuals with pathologic gambling do not consider the future consequences of their actions when they decide to give up treatment, suggesting ventromedial prefrontal cortex dysfunction.⁷⁵ Therefore, rash impulsiveness, sensation-seeking and strict regimentation, as well as poor spatial working memory and increased sensitivity to punishment, should be a target for additional specific interventions in pathologic gambling to enhance therapeutic adherence.

Finally, no association between the neurocognitive and self-report measures assessed and number of treatment sessions attended was identified. There are no studies about the relation between neurocognitive function and number of treatment sessions attended in pathologic gambling. Regarding the relation between self-reported impulsivity and number of treatment sessions attended, no studies have been published in the field of pathologic gambling. However, this association was studied by Patkar and colleagues⁷⁶ in a

sample of cocaine-dependent patients attending a 12-week, intensive outpatient treatment program, and they also failed to find an association between self-reported impulsivity and the number of treatment sessions attended. Therefore, more studies are needed in this respect.

To our knowledge, no other studies have examined the association between neuropsychological functions and dropout rates in pathologic gambling, so more research is needed to corroborate these findings.

Limitations

The present results must be assessed in the context of several limitations. First, most participants were slot-machine gamblers, and all of them were seeking treatment for this problem. This may affect the generalizability of our findings. Second, no follow-up data were available to confirm the maintenance of findings. Third, no control group was included, so we cannot conclude that the deficits that we observed are specific for pathologic gambling. Finally, the missing sample (i.e., individuals who were recruited and assessed in the pretreatment stage but who chose not to begin treatment) differed from the final sample in some measures of personality and executive functioning, so the final sample might have been biased toward a "healthier" group of people with pathologic gambling.

Conclusion

In sum, the present results suggest an association between overspending behaviour (extravagance in the present study) and sensitivity to reward in pathologic gambling. Treatment outcome, specifically dropout, was predicted by personality measures suggestive of deficits in self-regulation, (i.e., impulsiveness, understood as unreflective and careless behaviour) and (at a trend level) sensation-seeking, as well as by strict regimentation. Poor spatial working memory, suggesting executive dysfunction and sensitivity to punishment, reflecting insensitivity to the future, were also predictive of dropout. As far as we know, this is the first study that analyzes the effect of neurocognitive and self-report measures of impulsivity and self-regulatory deficits on treatment outcome measures of both dropout and relapse, as well as the first study that measures the effect of sensitivity to punishment (from a neurocognitive perspective) on treatment outcome. Very few studies have explored the relation between executive functioning and decision-making on the one hand, and self-report measures of impulsivity on the other, in pathologic gambling. As a personality trait, impulsivity may be difficult to modify. However, several studies suggest that "trait-oriented" interventions may optimize treatment effects in several mental disorders.⁷⁷ Apart from pharmacological interventions,⁷⁸ psychological interventions to modify impulsivity may include techniques to identify the impulse before acting, consider consequences and reflect on solutions. In addition, psychological interventions may be shorter and more intensive with motivational components to diminish the risk of dropout. Impulsivity in other mental disorders has also been addressed with Linehan's Dialectical Behaviour Therapy.⁷⁹ Although preliminary, these re-

sults may encourage future specific interventions addressed to diminish the risk of dropout during psychological treatment for pathologic gambling.

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References

1. Sharpe L. A reformulated cognitive-behavioral model of problem gambling. A biopsychosocial perspective. *Clin Psychol Rev* 2002; 22:1-25.
2. Koob GF, Le Moal M. Addiction and the brain antireward system. *Ann Rev Psychol* 2008;59:29-53.
3. Bechara A, Damasio AR, Damasio H, et al. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 1994;50:7-15.
4. Barkley RA. The executive functions and self-regulation: an evolutionary neuropsychological perspective. *Neuropsychol Rev* 2001;11: 1-29.
5. Bechara A, Damasio H, Tranel D, et al. Dissociation of working memory from decision making within the human prefrontal cortex. *J Neurosci* 1998;18:428-37.
6. Ragazzino ME. The contribution of the medial prefrontal cortex, orbitofrontal cortex, and dorsomedial striatum to behavioral flexibility. *Ann N Y Acad Sci* 2007;1121:355-75.
7. Moore TL, Schettler SP, Killiany RJ, et al. Effects on executive function following damage to the prefrontal cortex in the rhesus monkey (*Macaca mulatta*). *Behav Neurosci* 2009;123:231-41.
8. Rudebeck PH, Bannerman DM, Rushworth MF. The contribution of distinct subregions of the ventromedial frontal cortex to emotion, social behavior, and decision making. *Cogn Affect Behav Neurosci* 2008;8:485-97.
9. Kertzman S, Lowengrub K, Aizer A, et al. Stroop performance in pathological gamblers. *Psychiatry Res* 2006;142:1-10.
10. Marazziti D, Catena Dell'osso M, Conversano C, et al. Executive function abnormalities in pathological gamblers. *Clin Pract Epidemiol Ment Health* 2008;4:7.
11. Alvarez-Moya EM, Jimenez-Murcia S, Moragas L, et al. Executive functioning among female pathological gambling and bulimia nervosa patients: preliminary findings. *J Int Neuropsychol Soc* 2009; 15:302-6.
12. Brand M, Kalbe E, Labudda K, et al. Decision-making impairments in patients with pathological gambling. *Psychiatry Res* 2005;133:91-9.
13. Goudriaan AE, Oosterlaan J, de Beurs E, et al. Decision making in pathological gambling: a comparison between pathological gamblers, alcohol dependents, persons with Tourette syndrome, and

- normal controls. *Brain Res Cogn Brain Res* 2005;23:137-51.
14. Roca M, Torralva T, López P, et al. Executive functions in pathologic gamblers selected in an ecologic setting. *Cogn Behav Neurol* 2008;21:1-4.
 15. Franken IH, van Strien JW, Nijs I, et al. Impulsivity is associated with behavioral decision-making deficits. *Psychiatry Res* 2008;158:155-63.
 16. Bornovalova MA, Lejuez CW, Daughters SB, et al. Impulsivity as a common process across borderline personality and substance use disorders. *Clin Psychol Rev* 2005;25:790-812.
 17. Bechara A, Tranel D, Damasio H. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain* 2000;123:2189-202.
 18. Gray JA. The psychophysiological basis of introversion-extraversion. *Behav Res Ther* 1970;8:249-66.
 19. Dawe S, Loxton NJ. The role of impulsivity in the development of substance use and eating disorders. *Neurosci Biobehav Rev* 2004;28:343-51.
 20. Magid V, Maclean MG, Colder CR. Differentiating between sensation seeking and impulsivity through their mediated relations with alcohol use and problems. *Addict Behav* 2007;32:2046-61.
 21. Zuckerman M. *Sensation seeking: beyond the optimal level of arousal*. Hillsdale (NJ): Erlbaum; 1979.
 22. Kelly TH, Robbins G, Martin CA, et al. Individual differences in drug abuse vulnerability: d-amphetamine and sensation-seeking status. *Psychopharmacology (Berl)* 2006;189:17-25.
 23. Perkins KA, Lerman C, Coddington SB, et al. Initial nicotine sensitivity in humans as a function of impulsivity. *Psychopharmacology (Berl)* 2008;200:529-44.
 24. Steimer T, Escorihuela RM, Fernandez-Teruel A, et al. Long-term behavioural and neuroendocrine changes in Roman high-(RHA/Verh) and low-(RLA-Verh) avoidance rats following neonatal handling. *Int J Dev Neurosci* 1998;16:165-74.
 25. Hammelstein P. Faites vos jeux! Another look at sensation seeking and pathological gambling. *Pers Individ Dif* 2004;37:917-31.
 26. Slutske WS, Caspi A, Moffitt TE, et al. Personality and problem gambling: a prospective study of a birth cohort of young adults. *Arch Gen Psychiatry* 2005;62:769-75.
 27. Álvarez-Moya EM, Jimenez-Murcia S, Granero R, et al. Comparison of personality risk factors in bulimia nervosa and pathological gambling. *Compr Psychiatry* 2007;48:452-7.
 28. Potenza MN. Review. The neurobiology of pathological gambling and drug addiction: an overview and new findings. *Philos Trans R Soc Lond B Biol Sci* 2008;363:3181-9.
 29. Schalling D. Psychopathy-related personality variables and the psychophysiology of socialization. In: Hare RD, Schalling D, editors. *Psychopathic behaviour: approaches to research*. New York (NY): Wiley; 1978. p. 85-105.
 30. Baumeister RF, Vohs KD. *Handbook of self-regulation: research, theory, and applications*. New York (NY): The Guilford Press; 2004.
 31. Cloninger CR. *The Temperament and Character Inventory-Revised*. St. Louis (MO): Center for Psychobiology of Personality, Washington University; 1999.
 32. Strobel A, Wehr A, Michel A, et al. Association between the dopamine D4 receptor (DRD4) exon III polymorphism and measures of Novelty Seeking in a German population. *Mol Psychiatry* 1999;4:378-84.
 33. Mulder RT, Joyce PR. Relationships of the Tridimensional Personality Questionnaire to mood and personality measures for depressed patients. *Psychol Rep* 1994;75:1315-25.
 34. Acton GS. Measurement of impulsivity in hierarchical model of personality traits: implications for substance use. *Subst Use Misuse* 2003;38:67-83.
 35. Goudriaan AE, Oosterlaan J, De Beurs E, et al. The role of self-reported impulsivity and reward sensitivity versus neurocognitive measures of disinhibition and decision-making in the prediction of relapse in pathological gamblers. *Psychol Med* 2008;38:41-50.
 36. Forbush KT, Shaw M, Graeber MA, et al. Neuropsychological characteristics and personality traits in pathological gambling. *CNS Spectr* 2008;13:306-15.
 37. Adinoff B, Rilling LM, Williams MJ, et al. Impulsivity, neural deficits, and the addictions: the "oops" factor in relapse. *J Addict Dis* 2007;26(Suppl 1):25-39.
 38. Llewellyn DJ. The psychology of risk taking: toward the integration of psychometric and neuropsychological paradigms. *Am J Psychol* 2008;121:363-76.
 39. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed., text revised. Washington: The Association; 2000.
 40. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I disorders, Clinical Version (SCID-CV)*. Washington (DC): American Psychiatric Association; 1997.
 41. Lesieur HR, Blume SB. The South Oaks Gambling Screen (SOGS): a new instrument for the identification of pathological gamblers. *Am J Psychiatry* 1987;144:1184-8.
 42. Gutiérrez-Zotes JA, Bayón C, Montserrat C, et al. [Temperament and Character Inventory-Revised (TCI-R). Standardization and normative data in a sample of the general population] [Article in Spanish]. *Actas Esp Psiquiatr* 2004;32:8-15.
 43. Heaton RK. *Wisconsin Card Sorting Test manual*. Odessa (FL): Psychological Assessment Resources; 1981.
 44. Golden CJ. *Stroop Color and Word Test: Manual for clinical and experimental uses*. Chicago (IL): Stoelting; 1978.
 45. Lezak MD, Howieson DB, Loring DW. *Neuropsychological assessment*. 4th ed. New York (NY): Oxford University Press; 2004.
 46. Reitan RM. The validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills* 1958;8:271-6.
 47. Benton AL, Hamsher KD. *Multilingual Aphasia Examination*. Iowa city (IA): AJA Associates; 1983.
 48. Goldstein G, Nussbaum PD, Beers SR. *Neuropsychology*. New York (NY): Plenum Press; 1998.
 49. Artiola i Fortuny L, Hermsillo Romo D, Heaton RK, et al. [Handbook of norms and procedures for the neuropsychological battery in Spanish] [Book in Spanish]. Tucson (AZ): m Press; 1999.
 50. Wechsler D. *Wechsler Memory Scale, 3rd edition. Administration and Scoring Manual*. San Antonio (TX): Psychological Corporation; 1997.
 51. Conklin HM, Curtis CE, Katsanis J, et al. Verbal working memory impairment in schizophrenia patients and their first-degree relatives: evidence from the Digit Span Task. *Am J Psychiatry* 2000;157:275-7.
 52. Milner B. Interhemispheric differences in the localization of psychological processes in man. *Br Med Bull* 1971;27:272-7.
 53. Vandierendonck A, Kemps E, Fastame MC, et al. Working memory components of the Corsi blocks task. *Br J Psychol* 2004;95:57-79.
 54. Milton S, Crino R, Hunt C, et al. The effect of compliance-improving interventions on the cognitive-behavioural treatment of pathological gambling. *J Gamb Stud* 2002;18:207-29.
 55. Robson E, Edwards J. Gambling decisions: an early intervention program for problem gamblers. *J Gamb Stud* 2002;18:235-55.

56. Ledgerwood DM, Petry NM. Psychological experience of gambling and subtypes of pathological gamblers. *Psychiatry Res* 2006;144:17-27.
57. Wechsler D, Kaufman A. [WAIS-III: Wechsler Adult Intelligence Scale, 3rd edition] [Book in Spanish]. Madrid: TEA Ediciones SA; 1999
58. Jiménez-Murcia S, Álvarez-Moya EM, Granero R, et al. Cognitive-behavioral group treatment for pathological gambling: analysis of effectiveness and predictors of therapy outcome. *Psychother Res* 2007;17:544-52.
59. Zermatten A, Van der Linden M, d'Acremont M, et al. Impulsivity and decision making. *J Nerv Ment Dis* 2005;193:647-50.
60. Christodoulou T, Lewis M, Ploubidis GB, et al. The relationship of impulsivity to response inhibition and decision-making in remitted patients with bipolar disorder. *Eur Psychiatry* 2006;21:270-3.
61. Vassileva J, Gonzalez R, Bechara A, et al. Are all drug addicts impulsive? Effects of antisociality and extent of multidrug use on cognitive and motor impulsivity. *Addict Behav* 2007;32:3071-6.
62. Dougherty DM, Bjork JM, Harper RA, et al. Behavioral impulsivity paradigms: a comparison in hospitalized adolescents with disruptive behavior disorders. *J Child Psychol Psychiatry* 2003;44:1145-57.
63. Van Laere K, Goffin K, Bormans G, et al. Relationship of type 1 cannabinoid receptor availability in the human brain to novelty-seeking temperament. *Arch Gen Psychiatry* 2009;66:196-204.
64. Joyce PR, Mulder RT, Cloninger CR. Temperament and hypercortisolemia in depression. *Am J Psychiatry* 1994;151:195-8.
65. Etter JF, Pélissolo A, Pomerleau C, et al. Associations between smoking and heritable temperament traits. *Nicotine Tob Res* 2003;5:401-9.
66. Patton SR, Dolan LM, Powers SW. Differences in family mealtime interactions between young children with type 1 diabetes and controls: implications for behavioral intervention. *J Pediatr Psychol* 2008;33:885-93.
67. Harmsen H, Bischof G, Brooks A, et al. The relationship between impaired decision-making, sensation seeking and readiness to change in cigarette smokers. *Addict Behav* 2006;31:581-92.
68. Whiteside SP, Lynam DR. The five factor model and impulsivity: using a structural model of personality to understand impulsivity. *Pers Individ Dif* 2001;30:669-89.
69. Cunningham-Williams RM, Gattis MN, Dore PM, et al. Towards DSM-V: considering other withdrawal-like symptoms of pathological gambling disorder. *Int J Methods Psychiatr Res* 2009;18:13-22.
70. Liese BS, Beck AT. Back to basics: fundamental cognitive therapy skills for keeping drug-dependent individuals in treatment. *NIDA Res Monogr* 1997;165:207-30.
71. Gullo MJ, Dawe S. Impulsivity and adolescent substance use: Rashly dismissed as "all-bad"? *Neurosci Biobehav Rev* 2008;32:1507-18.
72. Dickman SJ. Functional and dysfunctional impulsivity: personality and cognitive correlates. *J Pers Soc Psychol* 1990;58:95-102.
73. Caci H, Nadalet L, Baylé FJ, et al. Functional and dysfunctional impulsivity: contribution to the construct validity. *Acta Psychiatr Scand* 2003;107:34-40.
74. Leiserson V, Pihl RO. Reward-sensitivity, inhibition of reward-seeking, and dorsolateral prefrontal working memory function in problem gamblers not in treatment. *J Gambl Stud* 2007;23:435-55.
75. Bechara A, Dolan S, Hindes A. Decision-making and addiction (part II): Myopia for the future or hypersensitivity to reward? *Neuropsychologia* 2002;40:1690-705.
76. Patkar AA, Murray HW, Mannelli P, et al. Pre-treatment measures of impulsivity, aggression and sensation seeking are associated with treatment outcome for African-American cocaine-dependent patients. *J Addict Dis* 2004;23:109-22.
77. Bruce KR, Steiger H. Treatment implications of Axis-II comorbidity in eating disorders. *Eat Disord* 2005;13:93-108.
78. Iancu I, Lowengrub K, Dembinsky Y, et al. Pathological gambling: an update on neuro-pathophysiology and pharmacotherapy. *CNS Drugs* 2008;22:123-38.
79. Linehan MM. *Cognitive-Behavioral Treatment of Borderline Personality Disorder*. New York (NY): Guilford Press; 1993.

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ZELDOX is not indicated in elderly patients with dementia. Caution should be used when treating geriatric patients with ZELDOX. The safety and efficacy of ZELDOX in children under the age of 18 have not been established.

In short-term, placebo-controlled schizophrenia clinical trials of a duration of up to 6 weeks, the most commonly observed adverse events associated with the use of ZELDOX (incidence of 5% or greater) and observed at a rate on ZELDOX at least twice that of placebo were somnolence (14% vs. 7%), extrapyramidal symptoms (14% vs. 8%), and respiratory tract infections (8% vs. 3%).

In short-term, placebo-controlled bipolar mania clinical trials, the most commonly observed adverse events associated with the use of ZELDOX (incidence of 5% or greater) and observed at a rate on ZELDOX at least twice that of placebo were somnolence (22.8% vs. 8.5%), akathisia (12.9% vs. 4.5%), extrapyramidal syndrome (13.6% vs. 4.9%), dizziness (10.7% vs. 4.0%) and dystonia (7.0% vs. 1.3%). Because of ZELDOX's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ZELDOX is contraindicated in patients with: known history of QT prolongation (including congenital long QT syndrome); recent acute myocardial infarction; or uncompensated heart failure. Pharmacokinetic/pharmacodynamic studies between ZELDOX and other drugs that prolong the QT interval have not been performed. An additive effect of ZELDOX and other drugs that prolong the QT interval cannot be excluded. Therefore, ZELDOX should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmias, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, propofol or tacrolimus. ZELDOX is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in their respective Product Monograph as a contraindication or a warning. ZELDOX is contraindicated in patients who are hypersensitive to ziprasidone or to any ingredient in the formulation or component of the container.

Serious Warnings and Precautions
Increased Mortality in Elderly Patients with Dementia
Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of 13 placebo-controlled trials with various antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6-fold increase in the death rate in the drug-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.



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