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The prevalence and features of schizophrenia among individuals with gambling disorder

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ABSTRACT

Background-objectives: Few studies have analyzed the comorbid presence of gambling disorder (GD) with schizophrenia, its sociodemographic correlates and clinical implications. This study estimated the prevalence of the dual diagnosis (GD with schizophrenia) and the differences in the profiles of patients with and without the dual condition.

Method: The sample included n = 3,754 patients consecutively accepted for treatment for GD. Sociodemographics, gambling-related variables, psychopathological state and personality traits were assessed and compared between the groups.

Results: The prevalence of schizophrenia within patients who met clinical criteria for GD was 4.4% (95% confidence interval: 3.8%–5.1%). Variables related to the dual presence of GD with schizophrenia were single marital status, lower education level, inactive working status, socioeconomic disadvantage, younger age, earlier onset of gambling problems, worse global psychopathological state and more dysfunctional personality profile (higher level in harm avoidance and lower level in cooperativeness, reward dependence, persistence and self-directedness).

Conclusion: The presence of schizophrenia among patients with GD was around 4 times higher than the prevalence rate estimated in the reference general population. The differences in the profiles of GD patients with and without schizophrenia suggest that individuals with the dual diagnosis condition require unique assessment considerations and tailored treatment interventions specifically designed for the clinical and functioning higher risk.

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1. Introduction

Gambling disorder (GD) is defined as a psychiatric condition involving continued engagement (repeated and uncontrollable behaviors) in problematic gambling activities despite adverse problems and distress (American Psychiatric Association, 2013). Individuals with GD present a significant diminished self-control over engagement in the behavior, as well as an urge or craving state prior to engaging in the gambling activity. The prevalence of GD worldwide is estimated at between 0.1% and 5.8% during the last year of the survey across five continents, and between 0.7% and 6.5% during lifetime (Calado and Griffiths, 2016).

1.1. Dual presence of GD with schizophrenia

GD has been associated with high rates of multiple comorbid psychiatric conditions (Dowling et al., 2015; Sundqvist and Rosendahl, 2019; Yakovenko and Hodgins, 2018; Yau and Potenza, 2015), including psychotic states and schizophrenia. Prevalence studies in samples of patients with psychosis have estimated rates of comorbidity with problematic or disordered gambling at between 12% and 19% (Aragay et al., 2012; Desai and Potenza, 2009), and concluded that people with psychosis are between 3 and 4 times more likely to have problematic or disordered gambling compared with the general population (Haydock et al., 2015). Reciprocal relationships between GD and schizophrenia have also been obtained in some epidemiological studies, which have outlined that problematic and impaired gamblers could be at an elevated risk of experiencing psychosis compared to the general population (Cassetta et al., 2018; Corbeil et al., 2019). The study of Kim and colleagues found that 7.2% of patients seeking treatment for GD met diagnostic criteria for psychosis (Kim et al., 2018b), while other studies have published rates of schizophrenia among problematic gambling and GD at around 5% (Bergamini et al., 2018; Cassetta et al., 2018; Peritogiannis et al., 2020). Based on these epidemiological data it is likely that GD and psychotic disorders co-occur frequently, and it seems that one disorder may exacerbate the symptoms of the other (Yakovenko et al., 2016). But the extent to which individuals with GD could also exhibit psychotic symptoms is a relatively novel field, and the specific implications of this dual-disorder condition on clinical gambling profiles remain to be understood. In fact, recent research has warned that the high rates of addictive behaviors within schizophrenia (including both problem and pathological gambling and substance-use disorders) could contribute to the undetected presence of GD in clinical practices, thus far unexamined in empirical studies (Fortgang et al, 2018, 2020). In addition, the presence of active psychotic episodes in the schizophrenia spectrum is typically an exclusion criterion in most studies carried out with GD samples. As a consequence, wide gaps exist between the relatively scarce research evidence and its application in practice and public policy settings.

Several converging empirical lines have tried to obtain evidence regarding the overlap between GD and other multiple psychiatric conditions, in terms of shared etiological factors (including neurobiological performance, heritability, individual and contextual factors), clinical manifestations and treatment outcomes. These studies are currently contributing towards identifying key components for the specific concurrence between GD and schizophrenia. Impulsivity (impaired control) is one of the factors recognized as a major problem for the presence of the dual-diagnosis condition (Hodgins and Holub, 2015; Kräplin et al., 2014; Lee et al., 2013; Ouzir, 2013). In fact, the diverse impulsivity domains (cognitive, affective and motor) have been considered essential features for the onset and progression of a wide array of psychopathological problems (Krueger and Eaton, 2015; Nolen-Hoeksema and Watkins, 2011; Robbins et al., 2012), and have led to it being considered as a transdiagnostic component within the well-known *impulsive compulsive disorder spectrum.* This construct has served to harbor diverse neuropsychiatric conditions (based on the inappropriate behaviors related to maladaptive impulses), and epidemiological studies have evidenced that it is common to observe the coexistence of multiple comorbid conditions within the spectrum and/or with other disorders also characterized by impaired control mechanism, such as GD with schizophrenia (Dowling et al., 2015; Lorains et al., 2011). For example, the study conducted by Aragay and colleagues within a sample of psychiatric inpatients shows that the in terms of comorbidity, the psychotic disorder spectrum achieve a higher prevalence of gambling problems than other psychiatric disorders (Aragay et al., 2012).

Second, neuropsychological research has also found similar dysfunctions in brain pathology and neurobiological processes that could contribute towards explaining the connection between GD and schizophrenia. Alterations in the motivation-reward systems, disturbances in the reward-directed behavioral circuitry (primary ventral striatum and medial prefrontral cortex) and abnormalities in neurotransmitter systems (such as dopamine, serotonin or glutamate) have been postulated as shared characteristics in both GD and psychotic disorders (Clark et al., 2019; Howes et al., 2015; Leicht et al., 2020; Potenza and Chambers, 2001; Ruiz et al., 2020; Selvaraj et al., 2014; Zack et al., 2020).

Third, multiple clinical manifestations are also common in GD and psychosis phenotypes. For example, the age of onset is typically in adolescence or young adulthood (Gin et al., 2020; Welte et al., 2015), particularly within the male sex. Personality profiles characterized by high levels of harm avoidance and low levels of self-directedness are also common in GD and the schizophrenic spectrum (Black et al, 2012, 2013; Sundqvist and Wennberg, 2015). High difficulties in emotion regulation and impairing cognitive biases around gambling activity have also been postulated as key features explaining the comorbid presence of GD with schizophrenia (Di Trani et al., 2017; Lawlor et al., 2020; Liu et al., 2020; Livet et al., 2020; Mallorquí-Bagué et al., 2018a, 2018b; Yakovenko et al., 2016). Finally, clinical studies have observed that the dual diagnosis of GD with schizophrenia is related to worse psychopathological state, evidenced by increased gambling severity (Kim et al., 2018a) and elevated risk for other psychiatric disorders (mainly substance and non-substance addictive behaviors) (Borras and Huguelet, 2007). But the number of studies analyzing the correlates of the dual diagnosis of GD and schizophrenia is low, and therefore emerging evidences must be considered with caution. New research is required to support (or refute) the pathophysiology of the concurrence of both psychiatric conditions, and to identify key features that may complicate the course, treatment adherence and overall prognosis of the illness.

1.2. Objectives

In summary, the comorbid presence of GD with dual diagnosis of schizophrenia constitutes a high-risk clinical group, which causes significant morbidity and disability to patients. But this vulnerable population remains understudied, and new research is required to assess the possible interactions of the schizophrenia on the gambling phenotypes. The objectives of this study were to estimate the prevalence of schizophrenia in a large sample of GD treatment seeking patients, and to assess differences in the sociodemographic and clinical profiles of patients who reported the dual diagnostic condition (GD plus psychosis).

Based on the available empirical research studies, we hypothesized a higher prevalence of psychosis among the GD patients (compared with the prevalence reported for the general population) and worse psychopathological functioning among patients with GD comorbid with schizophrenia.

2. Material and methods

2.1. Participants

This study analyzed a sample of $n = 3{,}754$ GD patients, accepted for treatment at the Pathological Gambling Outpatient Unit at University

Hospital of Bellvitge. This is a tertiary treatment service specialized in the assessment and treatment of gambling disorder and other behavioral addictions. All the participants were recruited between January 2005 and June 2020. Inclusion criteria in the study were age 18+ years and a sufficient level of education and cognitive capacity to complete the self-report measures. Exclusion criteria were the presence of an organic mental disorder, intellectual disability or neurodegenerative disorder (such as Parkinson's disease).

The participants in this study were consecutively attended at the treatment unit. All the patients routinely signed their acceptance for facilitating their data to the research studies approved by the Ethics Committee of the institution (the acceptance rate was 100%).

All the participants in the study met DSM-5 criteria for GD. The distribution of the sex was n = 3,421 men (91.1%) versus n = 333 women (8.9%), and the mean age was 42.0 yrs (SD = 13.5). The number of single patients was n = 1,541 (41.0%), versus n = 1,709 married (45.5%) and n = 504 divorced (13.4%). Most patients reported primary level of education or lower [*n* = 2,167 (57.7%) versus n = 1,352 with secondary level (36%) and n = 235 university level (6.3%)], and were employed (*n* = 2,152, 57.3%). Social position index was distributed as follows: n = 3,126 (83.3%) into mean-low to low, n = 400 (10.7%) into mean and n = 228 (6.0%) into mean-high to high. Mean age of onset of the problematic gambling was 29.2 yrs (SD = 11.0) and the duration of the GD 6.1 yrs (SD = 6.0).

2.2. Measures

Diagnostic Questionnaire for Pathological Gambling (according to DSM criteria) (Stinchfield, 2003). This questionnaire was developed as a self-report tool with 19 items coded in a binary scale (yes-no), with the aim of assessing the diagnosis of GD according to the DSM-IV-TR (American Psychiatric Association, 2000). Currently, this DSM-IV measure has been adapted to measure DSM-5 diagnostic criteria for GD (American Psychiatric Association, 2013) by removing the illegal acts criterion and using the cutoff score of 4 symptoms-criteria. The Spanish adaptation of this diagnostic questionnaire has demonstrated good psychometric properties (Jiménez-Murcia et al., 2009). The internal consistency for this scale in the study sample was adequate (α = 0.73).

Symptom Checklist-Revised (SCL-90-R) (Derogatis, 1994). This self-report questionnaire was developed to assess psychopathological state with 90 items covering a broad range of psychological symptoms and problems. It is structured in nine primary dimensions/scales (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism) and three secondary global indices (global severity index, GSI, total positive symptoms, PST, and positive discomfort index, PSDI). This study used the Spanish adapted version, which has proved to have good psychometric features (Gonzalez De Rivera et al., 1989). The internal consistency in the sample of this study is shown in Table 2, and ranged from adequate (α = 0.78, for paranoia scale) to excellent (α = 0.98 for the global indices).

Temperament and Character Inventory-Revised (TCI-R) (Cloninger et al., 1994). This self-report questionnaire was developed to assess seven primary personality traits through 240 items, based on Cloninger's multidimensional model. It covers 4 dimensions of the individual's temperament (novelty seeking, harm avoidance, reward dependence and persistence) and 3 dimensions of the individual's character (self-directedness, cooperation and self-transcendence). The Spanish version of TCI-R used in the study obtained very good psychometric indexes (Gutiérrez-Zotes et al., 2004). The internal consistency in the sample of the study (shown in Table 2) was between adequate (α = 0.71 for novelty seeking) and good (α = 0.87 for persistence).

Semi-structured clinical interview. It was used to assess additional information, including socio-demographics (sex, marital status, education level, employment status and social position) and gambling problem-related variables (such as the age of onset of the problematic gambling, duration of the GD and the accumulated debts due to gambling behaviors). The socioeconomic status (SES) was measured according to the Hollingshead's Four Factor Index, which provides a classification based on four domains (Hollingshead, 2011): marital status, retired/employed status, educational attainment and occupational prestige. Substantive and methodological reasons have justified the widely use of the SES in medicine and public health, principally because it provides a simple recipe for combining the standard sociological variables of education and occupation. The different gambling activities were also assessed, which encompass group gambling behavior in three broad categories: non-strategic gambling (including those games which involve little decision-making or skill, and therefore gamblers cannot influence the outcome: slot-machines, bingo and lotteries), strategic gambling (including games in which gamblers attempt to use their ability to predict the outcome: poker, sports/animal betting, craps, etc.), and both non-strategic plus strategic. Finally, the presence of lifetime comorbid disorders was also assessed. This semi-structured interview was conducted by psychologists and psychiatrists with extensive experience spanning over more than 15 years in the assessment and treatment of problematic gambling and GD. This complete tool has been described elsewhere (Jiménez-Murcia et al., 2006). In addition to the assessment of the clinical and sociodemographic variables included in the semi-structured interview, the clinicians confirmed the diagnosis of GD provided by the *Diagnostic Questionnaire for Pathological Gambling,* and also helped participants to complete the self-report questionnaires to guarantee the absence of missing data.

Diagnosis of schizophrenia. All the participants with a diagnosis of schizophrenia had been referred to our treatment unit from local Community Mental health Centers because the psychosis was associated with GD. The condition of schizophrenia had been diagnosed after assessment by psychiatrist specialists in the treatment of this mental condition, based on the DSM-IV and the DSM-5 criteria.

2.3. Statistical analysis

The statistical analyses were carried out with Stata16 for windows (Stata-Corp, 2016). The comparison between the groups defined by the presence-absence of schizophrenia was based on chi-square tests (χ^2) for categorical variables and the T-TEST for independent samples for quantitative measures.

The significance tests were complemented with the estimation of the effect sizes through the Cohen's-*d* measure, considered null for $|d|<$ 0.20, low-poor for $|d|>0.20$, moderate-medium for $|d|>0.50$ and large-high for $|d|>0.80$) (Cohen, 1988; Kelley and Preacher, 2012).

To control the increase in the Type-I error due to the multiple statistical comparisons, the Finner method was used, a procedure considered within the familywise error rate stepwise techniques which is more effective than the classical Bonferroni correction (Finner, 1993; Finner and Roters, 2001).

2.4. Ethics

All procedures were carried out in accordance with the Declaration of Helsinki of 1975, as revised in 2000. The data analyzed in this study were recruited during different research projects approved by the Ethics Committee of the Bellvitge University Hospital (Refs: PR241/11, PR286/14, PR329/19, PR338/17 and PR393/17). All subjects were informed about the study and all provided informed consent.

3. Results

3.1. Prevalence of schizophrenia in the study

The number of participants who with schizophrenia was n = 166, resulting in a prevalence rate equal to 4.42% [95% confidence interval (95%CI): 3.76%–5.08%]. At the time of the study, the number of

patients with schizophrenia was n = 132 (prevalence = 3.52; 95%CI: 2.93%–4.11%), while n = 151 reported the presence of these symptoms in the past (prevalence = 4.02; 95%CI: 3.39%–4.65%). Fig. 1 contains the line-chart displaying the evolution of the prevalence of psychosis in the study, which suggests an increasing linear trend.

3.2. Variables related to the presence of schizophrenia in the study

Table 1 shows the comparison of the patients with and without schizophrenia for the sociodemographic features, the age of onset of the problematic gambling and the duration of the GD. The presence of schizophrenia was related to a higher likelihood of being single, lower education level, unemployment status, and lower social position indexes. Patients with schizophrenia were also younger and reported earlier onset of the gambling problems.

Table 2 shows the comparison between the groups for the clinical measures analyzed in this work. Compared to patients without schizophrenia, the comorbid presence of schizophrenia and GD was related to worse psychopathological state (higher mean scores in the SCL-90R scales, except for hostility) and more dysfunctional personality profile (higher mean score in the harm avoidance trait, and lower means in reward dependence, persistence, self-directedness and cooperativeness) (Fig. 2). In addition, patients with schizophrenia increased the likelihood of non-strategic games as the preferred form of gambling and of tobacco use. No differences between the groups were found for the GD severity (measured with the number of DSM-5 criteria), the novelty seeking and self-transcendence personality traits, the gambling platform (offline versus online), the cumulated debts due to the gambling activity and the alcohol and drugs consumption.

4. Discussion

This study analyzed the presence of schizophrenia among patients seeking treatment for GD, as well as the differences in the gambling phenotypes comparing participants with and without schizophrenia. Prevalence of lifetime psychosis was 4.4%, and variables related to the dual presence of GD with psychosis were being single, lower education, unemployed status, lower social position indexes, younger age, earlier onset of the gambling problems and worse psychopathological state.

The study of the comorbidity of GD with other psychiatric conditions has mainly focused on substance-related problems (Graham, 2009; Grant and Chamberlain, 2020), but few studies have been conducted on the concurrence of GD with major psychiatric illness such as psychosis. To our knowledge, the first published study analyzed data recruited from n = 337 outpatients on the schizophrenic spectrum, and observed a prevalence of problematic or disordered gambling of around 20% (about 10% met criteria for GD and an additional 10% met criteria for lower severity but impairing features related with the gambling behavior) (Desai and Potenza, 2009). Next, the study of Haydock and colleagues conducted in a sample of n = 442 adults who met clinical criteria for psychosis obtained a prevalence of 4% for low-risk gambling activity, and 12% of the participants were classified between moderate to high gambling (Haydock et al., 2015). This study also found that a higher risk of gambling within the psychotic spectrum was related to lower education levels and lower socioeconomic status (as we have also observed in our research). Other empirical studies have published rates of schizophrenia among high-risk gamblers and GD patients at around 5%, an estimate four times higher than prevalence of psychosis in the reference general population (Bergamini et al., 2018; Cassetta et al., 2018; Kim et al., 2018a, 2018b; Peritogiannis et al., 2020).

The prevalence of schizophrenia in the GD patients analyzed in our study (equal to 4.4%) is consistent with the rates previously published, and our estimation is around 4 times higher than the prevalence of schizophrenia in the Spanish general population (around 1%) (Moreno-Küstner et al., 2018). This result can be interpreted in two ways: a) GD constitutes a highly vulnerable group for experiencing psychosis; and b) the presence of psychotic states represents high vulnerability to addictive behaviors, including gambling. This latter situation is particularly relevant, since a growing number of reports have related second-generation antipsychotics [such as aripiprazole (ARI), a partial D2 receptor agonist] with new onset gambling behavior or with increases in the severity of such behaviors (Corbeil et al., 2020; Gaboriau et al., 2014; Grall-Bronnec et al., 2016; Miuli et al., 2020; Smith et al., 2011). These studies suggest that the ARI-induced gambling disorder could be explained by the altered sensitization of dopamine receptors in certain genetically susceptible individuals, mostly in the early course of schizophrenia-related psychotic disorders. Studies with Parkinson's disease patients treated with dopaminergic agonistics for motor symptom management in early stages [such as pramipexole (PPX) and ropinirole (ROP)] have observed increased risk of developing behavioral complications within the impulse control disorder spectrum (including GD) (Gatto and Aldinio, 2019; Molde et al., 2018). Among Parkinson's disease with GD diminished striatal D2/D3 receptor level and increased in mesolimbic dopaminergic agonists tone has been reported, leading to an imbalance in the cortico-accumbens network implicated in reward signaling and behavioral changes (Buckholtz et al., 2010). It has also been observed that iatrogenic GD among Parkinson's disease patients may be mediated at least partly by increased activation of the intra-cellular signaling proteins GSK3β and CREB in the striatum (Cocker et al., 2019), and that the dopaminergic mesocorticolimbic system provides a role for shift behaviors in response to changing stimulus-reward contingencies (Houeto et al., 2016). But the results

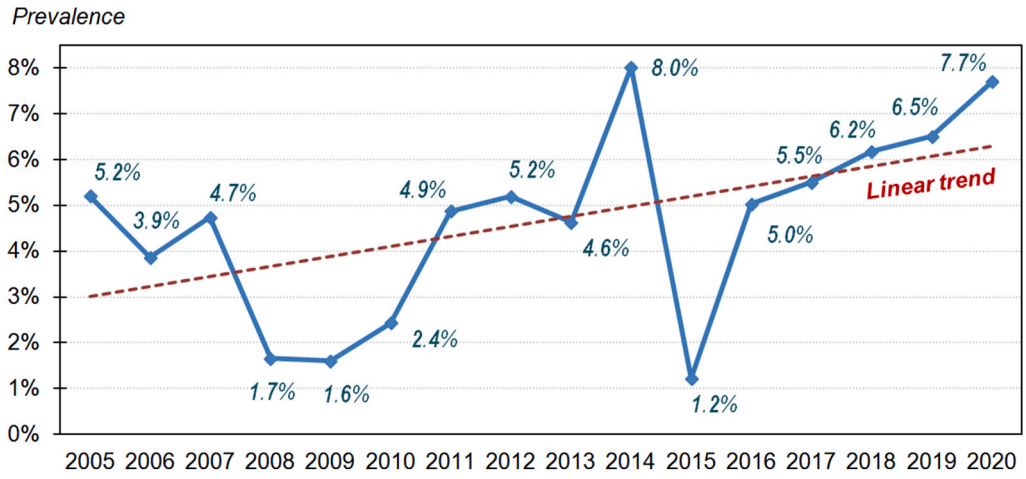

Fig. 1. Prevalence of patients with lifetime schizophrenia during the years 2005–2020 (n = 3,754).

Table 1
Descriptive for the sample and comparison between the groups.

		Total sample		Schizophrenia					
		(*n* = 3,754)		Absent (*n* = 3,588)		Present (*n* = 166)			
		n	%	*n*	%	*n*	%	*p*	|*d*|
Sex	Women	333	8.9%	319	8.9%	14	8.4%	.840	0.02
	Men	3421	91.1%	3269	91.1%	152	91.6%		
Marital status	Single	1541	41.0%	1428	39.8%	113	68.1%	**<.001**[a]	**0.59**[b]
	Married	1709	45.5%	1677	46.7%	32	19.3%		**0.61**[b]
	Divorced	504	13.4%	483	13.5%	21	12.7%		0.02
Education	Primary	2167	57.7%	2060	57.4%	107	64.5%	**.023**[a]	0.14
	Secondary	1352	36.0%	1297	36.1%	55	33.1%		0.06
	University	235	6.3%	231	6.4%	4	2.4%		0.20
Employed	Unemployed	1602	42.7%	1469	40.9%	133	80.1%	**<.001**[a]	**0.87**[b]
	Employed	2152	57.3%	2119	59.1%	33	19.9%		
Social position	High	54	1.4%	54	1.5%	0	0.0%	**<.001**[a]	0.17
	Mean-high	174	4.6%	172	4.8%	2	1.2%		0.21
	Mean	400	10.7%	393	11.0%	7	4.2%		0.26
	Mean-low	1213	32.3%	1176	32.8%	37	22.3%		0.24
	Low	1913	51.0%	1793	50.0%	120	72.3%		0.47
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*P*	|*d*|	
Chronological age (yrs-old)	42.02	13.45	42.12	13.58	39.83	10.19	**.032**[a]	0.19	
Age of onset GD (yrs-old)	29.20	10.98	29.29	11.02	27.25	9.83	**.019**[a]	0.20	
Duration GD (years)	6.13	6.03	6.10	5.99	6.81	6.87	.138	0.11	

Note. SD: standard deviation.
[a] Bold: significant comparison.
[b] Bold: effect size into the range mild-moderate (|*d*|>0.50) to high-large (|*d*|>0.80).

Table 2
Comparison of the clinical measures.

		Schizophrenia					
		Absent (*n* = 3,588)		Present (*n* = 166)			
	α	*Mean*	*SD*	*Mean*	*SD*	*p*	|*d*|
DSM-5 criteria for GD	.727	7.19	1.52	7.37	1.43	.141	0.12
SCL-90R Somatization	.904	0.99	0.81	1.15	0.77	**.013**[a]	0.20
SCL-90R Obsessive-compulsive	.877	1.19	0.81	1.44	0.84	**<.001**[a]	0.31
SCL-90R Personal sensitivity	.869	1.06	0.81	1.52	0.95	**<.001**[a]	**0.52**[b]
SCL-90R Depression	.906	1.56	0.89	1.76	0.92	**.005**[a]	0.22
SCL-90R Anxiety	.890	1.06	0.79	1.31	0.88	**<.001**[a]	0.31
SCL-90R Hostility	.849	0.96	0.83	1.03	0.84	.307	0.08
SCL-90R Phobic anxiety	.819	0.50	0.66	0.93	0.82	**<.001**[a]	**0.58**[b]
SCL-90R Paranoia	.782	0.96	0.78	1.34	0.85	**<.001**[a]	0.46
SCL-90R Psychotic	.854	0.94	0.74	1.26	0.91	**<.001**[a]	0.38
SCL-90R GSI	.980	1.10	0.69	1.36	0.76	**<.001**[a]	0.36
SCL-90R PST	.980	47.46	20.99	52.32	22.84	**.004**[a]	0.22
SCL-90R PSDI	.980	1.92	0.58	2.14	0.62	**<.001**[a]	0.37
TCI-R Novelty seeking	.707	110.13	13.01	108.80	10.20	.193	0.11
TCI-R Harm avoidance	.815	101.08	16.10	108.16	13.95	**<.001**[a]	**0.51**[b]
TCI-R Reward dependence	.768	98.14	13.86	94.11	11.34	**<.001**[a]	0.32
TCI-R Persistence	.867	108.41	18.72	103.74	17.96	**.002**[a]	0.25
TCI-R Self-directedness	.847	126.27	19.62	120.83	16.80	**<.001**[a]	0.30
TCI-R Cooperativeness	.807	129.77	15.44	125.04	13.82	**<.001**[a]	0.32
TCI-R Self-transcendence	.830	63.64	14.14	65.20	13.63	.163	0.11
		n	%	*n*	%	*p*	|*d*|
Gambling preference	Non-strategic	2576	71.8%	130	78.3%	**.012**[a]	0.15
	Strategic	421	11.7%	7	4.2%		0.28
	Mixed	591	16.5%	29	17.5%		0.03
Gambling platform	Offline	3368	93.9%	161	97.0%	.098	0.15
	Online	220	6.1%	5	3.0%		
Debts due to gambling behavior	1797	50.1%	71	42.8%	.065	0.15	
Tobacco use/abuse	2202	61.4%	132	79.5%	**<.001**[a]	0.41	
Alcohol use/abuse	574	16.0%	27	16.3%	.927	0.01	
Illegal drugs use/abuse	383	10.7%	24	14.5%	.125	0.11	

Note. SD: standard deviation. α: Cronbach's alpha.
[a] Bold: significant comparison.
[b] Bold: effect size into the range mild-moderate (|*d*|>0.50) to high-large (|*d*|>0.80).

suggesting a relationship between dopamine replacement therapies and the emergence of GD are still controversial and cannot prove the causality or the strength of the association (Heiden et al., 2017; Voon et al., 2017). In addition, the management of the gambling related symptoms in these patients is challenging, due the few effective treatment alternatives and/or counteractive strategies (Jeon and Bortolato, 2020).

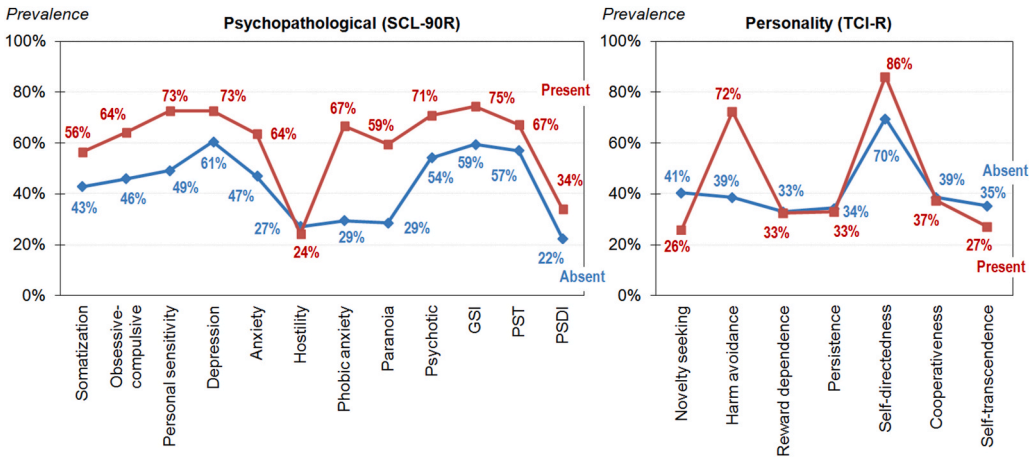

Fig. 2. Prevalence of patients outside the normative ranges (n = 3,754).

More details in future case reports and well-powered prospective controlled studies are required to draw reliable evidence about the specific underlying mechanisms (including individual and environmental vulnerability factors) explaining the concurrence of GD with schizophrenia.

In this study, the group of patients who exhibited gambling disorder with schizophrenia reported greater psychological distress, with higher mean scores in all the SCL-90R scales (except for hostility). This result is congruent with previous research that outlined that GD with psychosis constitutes a highly vulnerable condition which increases the risk of other poly-comorbid psychopathological conditions and suicidality (Yakovenko et al., 2016), as well as greater chasing and lower functioning (Yakovenko et al., 2018). And since previous studies have also related the concurrence of multiple psychiatric problems with worse treatment outcomes (Merkouris et al., 2016), it is crucial that clinical settings explore the presence of diverse symptoms among patients with GD with the aim of incorporating specific strategies to manage and reduce their impacts. Ultimately, the adequate identification of the diverse psychological processes underlying dysfunctional conditions such as addictive disorders (both substance use disorders and behavioral addictions) has relevant benefits during the treatment, since intervention on this specific mechanism (compared to therapies targeting a single disorder) contribute towards alleviating both primary psychopathologies and secondary concurrent psychiatric conditions (Krueger and Eaton, 2015). GD is a highly disabling mental condition which carries a great deal of stigma, and its developmental course is greatly worsened by the concurrent presence of schizophrenia (a mental health condition which impairs individuals' capacity to separate illusion from reality). Evidence-based integrative intervention plans should be specifically developed to treat the dual presence of GD with psychotic symptoms, addressed to the full range of physical and emotional problems, as well as the environmental influences that affect the patients' health. These healing-oriented holistic programs should include medication for correcting chemical imbalances, as well as other strategies to increase self-control and reduce impulsivity (such as training in working memory and response inhibition), to improve emotional regulation, to prevent or reduce chronic stress and to increase social skills. Pilot studies in this area have reported the beneficial effects of treatments particularly developed for patients with dual diagnoses of schizophrenia and GD focused on training reactive and proactive control, the ability to stop in response to a stop-stimulus, and the capacity to anticipate and prepare for a stop (these interventions have resulted in significant decreases in the number of gambling episodes and the amount of money spent on gambling) (Echeburúa et al, 2011, 2017). These studies have, however, failed to measure psychotic symptoms as an outcome of the treatments. Since few studies have analyzed the moderating role of psychiatric disorders as moderators of the efficacy of GD interventions (Dowling et al., 2016), future research is required to assess outcomes of treatments specifically matched to client GD with other comorbid conditions. For example, since emerging evidence suggest that association between schizophrenia and GD could endorse motivations for engaging in gambling activity and motivations for persisting in gambling that may be unique and not present in GD without schizophrenia (Yakovenko et al., 2016), therapeutic plans should focus in these specific mechanisms to achieve gambling abstinence and avoid relapses.

Regarding substance use, the only difference between the groups defined in our study based on the presence/absence of schizophrenia was for smoking habit (no differences emerged for the prevalence of alcohol and drugs consumption). It must be outlined that the previous cumulated evidences within this area are unambiguous: while some studies have observed that individuals with GD and psychosis are not more likely to be diagnosed with alcohol or substance use disorder (Kim et al., 2018a), other research has associated the presence of this dual-diagnostic condition with high rates of poly-substance use (Rash et al., 2016). It should be outlined that empirical studies exploring the specific mechanisms explaining the higher rates of substance use within patients with GD and schizophrenia have identified delay discounting function as a mediational link. Delay discounting refers to the loss of subjective value of a specific reward as a function of delay (it describes the concrete process by which individuals forego a larger later reward for a smaller earlier reward) (MacKillop et al., 2011). This measure represents one important type of choice impulsivity that may be informative regarding brain reward circuitry as preference for future wards (it involves the preferential selection of smaller sooner rewards over larger later rewards). Since adaptive reward processing is crucial for successful motivation, goal-directed behavior and goal-attainment across most domains of life, poor performance on delay discounting may directly impact the ability to appreciate the necessity of long-term events and planning for future. Based on the links between delay discounting to clinically relevant constructs (like treatment outcomes), this process has been suggested to be a trans-diagnostic feature underlying severe mental problems (Hamilton et al., 2015), including GD (Kyonka and Schutte, 2018) and schizophrenia (Horan et al., 2017). A current study aimed to investigate the relationship between GD and delay discounting in a sample of schizophrenia patients found that this choice impulsivity could represent a potential mechanism into the association between the dual comorbid condition (GD with schizophrenia) and substance (or poly-substance) use, but only among males (Fortgang et al., 2018). Concretely, the authors of this study observed that within the men subsample: a) the presence of GD was related with increased rates of delay discounting (compared with non-gambling); b) individuals with history of treatment for substances or poly-substances use

registered higher delay discounting (compared with non-consumers); and c) this may suggest that men who exhibit schizophrenia with substance related problems could be characterized by higher levels in some impulsivity domains, that positive reinforcement mechanisms could play a smaller role in the addictive processes within schizophrenia populations (compared to other diagnoses), and that lower levels of these features could create sensitivity to addiction. But these results should be considered with caution: mixed findings have been obtained in studies assessing the role of delay discounting, and these inconsistent evidences could be explained by the occurrence of comorbidity in chronic samples (Wang et al., 2020). Therefore, further studies should assess how choice impulsivity varies across psychiatric disorders and comorbid conditions, including the pathways between delay discounting and clinical manifestations among GD with schizophrenia.

Regarding personality traits, results obtained in this study are also consistent with previous research using the TCI-R questionnaire, which have reported higher levels in harm avoidance and lower scores in cooperativeness, self-directedness, reward dependence and persistence within the schizophrenic spectrum. High harm avoidance is characterized by excessive worrying, pessimism and shyness, as well as the tendency to be fearful, doubtful and easily fatigued; in this sense, high harm avoidance measures the tendency to respond with overall attenuation to aversive stimuli and to avoidant behavior due to the vulnerability to criticism and rejection, and it has been considered as a predictor of poor quality of life in the schizophrenic spectrum. Low cooperativeness describes the character of individuals as little empathic and callous, with a tendency to intolerance, social disinterest, unhelpfulness and revengefulness. It has been observed that high levels in harm avoidance and low levels in cooperativeness constitute a psychopathological related endophenotype of schizophrenia patients, which can contribute towards explaining some social dysfunctions observed in these patients (Fresán et al., 2015). High harm avoidance and low cooperativeness, low persistence and low self-directedness have also been reported within patients with schizophrenia compared with control subjects (Vrbova et al., 2017), and this specific profile has been linked to a higher risk of neurological soft signs (a well-known biological marker of schizophrenia, defined as minor neurological abnormalities without a definite localization in the brain, including expressions of simple sensory integration, disinhibition signs, motor coordination, complex motor sequencing) (Galindo et al., 2016; Mechri et al., 2010; Zhao et al., 2014).

Related to the personality profile identified in the GD with schizophrenia group, some studies have also explored the relationships between imaging/brain markers, personality features and its contribution to understanding the underpinnings of mental illness (Farde et al., 2018). With regard to psychosis-related traits, striatal amphetamine-induced dopamina release has been related with schizotypal personality traits and schizophrenic negative symptoms [such as social distress (discomfort in social situations and difficulty making/-keeping friendships), flat emotions or limited/inappropriate emotional responses, and incorrect interpretation of events] (Roiser et al., 2013; Woodward et al., 2011). Specific genes such as DRD4 and COMT (which regulate dopamine activity) have also been related with specific personality traits also related with the pathogenesis of psychotic disorders (concretely, sensation-novelty seeking and openness to experiences could be mediated by the pathophysiological mechanisms at the neurotransmitter level among psychotic patients) (Peritogiannis, 2015). A recent study has also found that polygenic risk for schizophrenia is associated with disordered gambling, concluding that that common genetics factors could have pleiotropic effects on both psychiatric conditions (one disorder could act as an intermediate phenotype providing a crucial link in a causal chain and setting the required conditions to facilitate the onset of the second disorder) (Piasecki et al., 2019). Anyway, the results of this study must be adequately contextualized. Two groups of patients were compared in this work: GD without schizophrenia and GD with schizophrenia. The different personality profile associated with the dual comorbid condition, although being consistent with previous results reported in samples within the schizophrenic spectrum, does not evidence a more severe dysfunctional personality profile than usual pronounced endophenotype traits of personality among schizophrenia patients. Future studies should detail the potential similarities and differences of the complete clinical profiles (symptoms, psychopathological distress and personality traits) comparing GD schizophrenia versus non GD schizophrenia patients.

Our study did not find a relationship between the concurrent presence of schizophrenia with GD and a greater level of gambling behavior. This result is not consistent with previous research, which observed higher gambling severity within problematic gamblers with psychosis (Fortgang et al., 2020). However, it is important to outline that this potential relationship could be explained by the mediating role of impulsivity, as stated by previous research (Kim et al., 2018b). Since our study did not include a measure of the impulsivity levels, it was not possible to assess this potential mediational role. Therefore, the absence of a direct relationship between the presence of schizophrenia and greater gambling severity levels in our study does not exclude an indirect effect through some impulsivity domain.

Finally, our study also obtained a higher likelihood for non-strategic gambling forms (slot-machines, bingo and lotteries) among the group of GD with comorbid psychosis state. Previous studies have outlined that the selection of a concrete form of gambling is clinically significant and provides a means of subtyping individuals with GD (Odlaug et al., 2011; Stevens and Young, 2010). It has been observed that two socioeconomic factors contribute towards increasing the odds of reporting non-strategic high-chance games: lower educational levels and disadvantaged socioeconomic status (Moragas et al., 2015), features characteristics of the group with the dual GD and psychosis condition. On the other hand, non-strategic gambling has also been related to disadvantageous cost-benefit decision-making (Jiménez-Murcia et al., 2020). Previous researchers reveal that patients with schizophrenia experience deficits in decision-making tasks, expressed by a systematic failure in the contingency learning required to distinguish between advantageous and disadvantageous selections when valuing frequencies and magnitudes of loss and gains (these patients show reinforcement learning deficits incorporating experiences of outcomes on previous tasks to assess the expected value of each new selection) (Boka et al., 2020; Brown et al., 2015; Kim et al., 2016). These characteristics of decision-making under risk typical of psychotic states could lead to a preferred non-strategic gambling, characterized by little deliberation or few skills (in these games, the potential result is totally dependent on chance).

4.1. Limitations and strengths

This study should be interpreted in the context of some limitations. First, the cross-sectional nature of the data, which did not allow cause-effect relationships to be determined. Second, this work was conducted within a sample of patients who met clinical criteria for GD, and therefore our findings cannot be generalized to complete original populations of problematic or non-treatment-seeking individuals. Third, among schizophrenia patients the antipsychotic medication and the presence/impact of the negative symptoms was not available (future research should examine the potential interactive contribution of these measures to the clinical profile and the GD treatment efficiency). Finally, this work was based on the comparison of two groups (GD versus GD with schizophrenia), and the lack of a non-gambling schizophrenia group do not allow to know if the phenotype obtained in the dual condition is actually more accurately characterizing schizophrenia rather than a comorbid picture. However, it must be outlined that our aim was to assess the differential characteristics related with the presence of schizophrenia among GD patients, since knowing this particular profile is required for developing more inclusive GD treatment approaches (patients with schizophrenia attended in centers specialized in GD treatment usually receive the standardized programs initially developed for patients without the dual comorbid condition). It is also important to

note that GD and schizophrenia share some common characteristics, such as specific community and sociodemographic features (poor academic performance and low socioeconomic status), personality traits (high scores in impulsivity and harm avoidance and low scores in persistence and self-directedness), and clinical features [such as cognitive difficulties (impaired decision making and planning), and the presence of multiple comorbid psychopathologies (such as substance related disorders, anxiety and depression)]. Therefore, it is relevant to assess the increased risk in the GD with schizophrenia profile compared to only GD for developing adequate assessment tools and personalized intervention plans.

The strengths of the study were its novelty (few research projects to date have explored phenotypes for GD with schizophrenia), the clinical origin of the data, the large sample size and the sampling procedure (consecutive patients over a long period).

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Declaration of competing interest

All authors declare no conflicts of interest.

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