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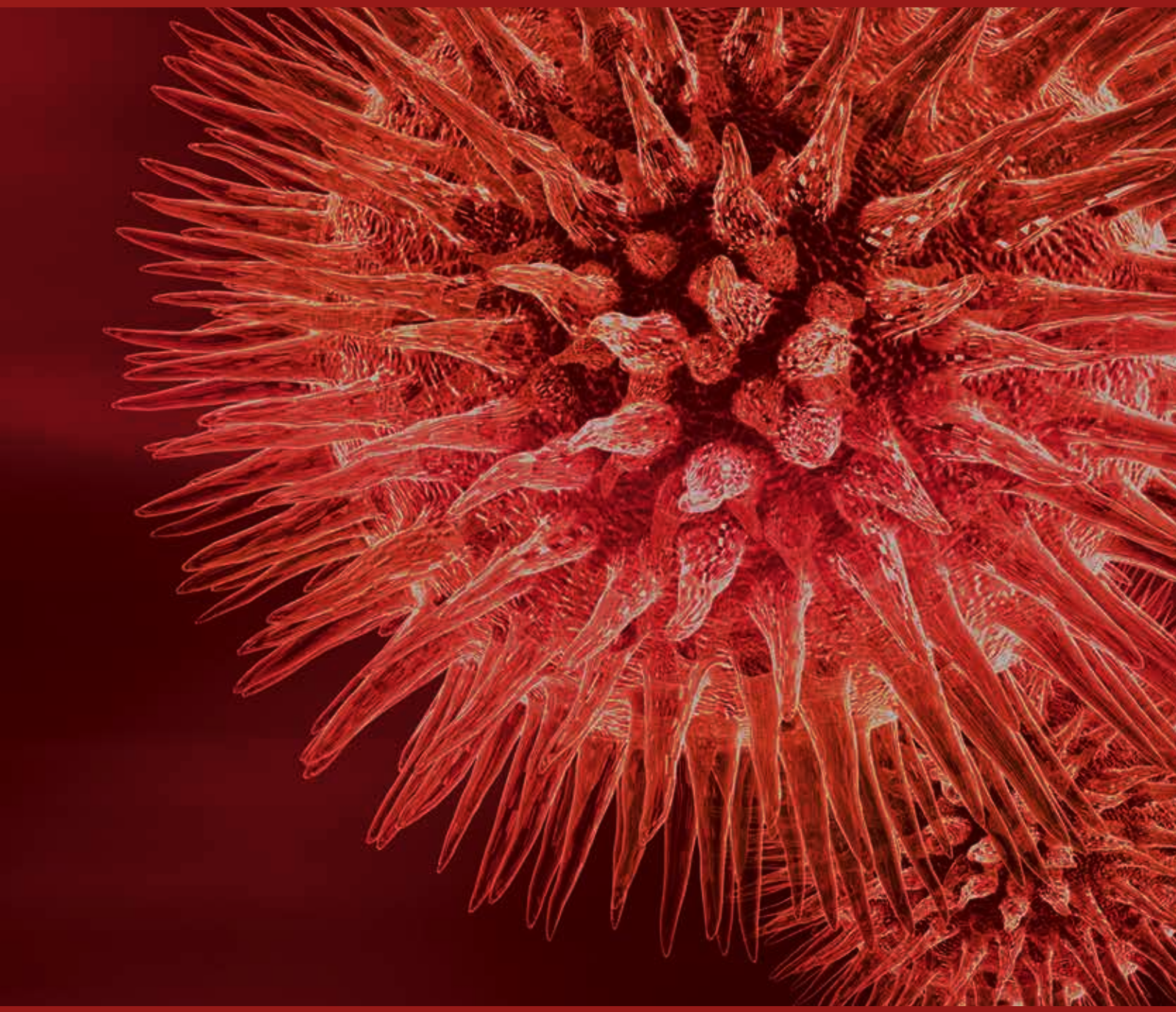
Novel Psychoactive Substances and Behavioral Addictions

Guest Editors: Giovanni Martinotti, Ornella Corazza, Sophia Achab, and Zsolt Demetrovics



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Editorial

Novel Psychoactive Substances and Behavioral Addictions

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The present special issue addresses two key areas, which at first sight may not appear to be particularly related to each other. Their novelty, however, connects them tightly. The appearance of these two issues has, on one hand, required and promoted a renewal of the perspective in addiction science and, on the other hand, could facilitate the rethinking of practical, therapeutic, and preventive interventions. Thus, both areas share a main common aspect: they raise new issues that need to be addressed in the field of addictions and, as such, force us to reconsider former approaches.

One of the focuses is the emergence of novel psychoactive substances, especially in relation to the fast moving and the potentially unlimited nature of their online market [1]. A "novel psychoactive substance" has been legally defined by the European Union as a new narcotic or psychotropic drug, either in pure form or in a preparation, that is not scheduled under the Single Convention on Narcotic Drugs of 1961 or the Convention on Psychotropic Substances of 1971, but which may pose a public health threat comparable to substances listed in the above-mentioned conventions (Council of the European Union decision 2005/387/JHA) (UNODC, 2014).

From the psychedelic movements of the 1960s until the beginning of the 21st century, there was hardly any change regarding the most used drugs. In addition to cannabis, heroin, and cocaine, primarily LSD and, to a lesser extent, magic mushrooms among hallucinogenic drugs and amphetamine basically covered the significant range of substances of abuse. Although the presence of ecstasy from the end of the 1980s had brought some moderate changes, it can be stated that researchers and prevention and treatment professionals could work in a relatively stable environment throughout decades. Users basically used the same drugs and sought help for similar problems, and therefore studies could systematically grow and support the preventive and clinical efforts.

The novel psychoactive substances, however, that began to spread after the millennium [2–4] have fundamentally reorganized this apparently stable situation. Since then, new substances have constantly been appearing on the market. It is not rare that there is no time to even identify a new drug before another substance takes its place on the market and they might disappear a few days, weeks, or months later, while newer ones appear. This extremely rapidly changing situation concerning drug use and drug market set new challenges for professionals. We have to describe the use of drugs on which we have very limited knowledge. Not only is the chemical description of these substances often unavailable, but often we do not even know their street names. The effects of drugs should be explored while their name and nature are unknown to both the dealer and the user. We have to estimate the risks associated with substances without being familiar even with their most basic characteristics. We have to provide information to potential users of these drugs and we hardly know anything about them or treat unknown side effects or overdoses.

It is no surprise that in this rapidly changing environment initiatives have been launched [5] that apply new data

collection methods and aim to gather information as fast as possible and share this knowledge within target groups via new effective tools [2, 3]. The opportunities provided by the developments in the field of info communication technologies, the Internet, and smartphones could be of great value for this aspect. All these factors, in fact, contribute to the rethinking and renewal of data collection and data analysis methods, the reallocation of resources, and the reconsideration of prevention tools and efforts, as well as the implementation of other types of interventions. The present special issue, on one hand, intends to make a contribution for facing these challenges.

On the other hand, during the past few years, "new addictions" have emerged in addition to the new drugs. These addictions are actually not a new problem of course, but the formerly described disorders appear in a new interpretative framework. In the past decades, but especially in the past few years, the opinion that the range of addictive disorders should not be reduced to psychoactive substances-related dependencies has been strengthened. In line with this, scientific literature on addictions has begun to deal with a growing number of phenomena, originally not classified as addictive disorders, but with important psychological and social consequences [6–8].

Among behavioral addictions gambling disorder represents the main area, giving the large diffusion of gambling. With the increase in availability of gambling products across the world and the increased exposure to gambling advertisements both on TV and on mobile platforms, we are currently faced with a larger number of people across the globe who are using gambling as a recreational pursuit.

Issues of current significance in the gambling world are the targeting of children and adolescents by the gambling industry, the targeting of older people by larger casinos offering company and distraction but focusing on a vulnerable group, and the targeting of female and indigenous populations, who are being reached by specific advertising campaigns across most of the world.

Besides the new interpretation of gambling disorder, formerly classified as an impulse control disorder, new interpretations of numerous other disorders from the addiction perspective have also been raised. Among these are other impulse control disorders, eating disorders, specific sexual disorders, and, among other problems officially not classified as disorders, the Internet addiction, online gaming, exercise addiction, and many others. It is becoming more and more common to see the expressions of behavioral addiction or nonsubstance use addiction [9, 10]. The formal expansion of the range of addictive disorders to the direction of addictions not related to chemical substances has eventually been brought by the publishing of DSM-5 [11]. In this edition of the manual, the former section on "*Substance-Related Disorders*" has been replaced with "*Substance-Related and Addictive Disorders*." This chapter indeed includes a subchapter titled "*Non-Substance-Related Disorders*." Although addiction experts could classify several disorders belonging here, at the moment the only official member of this group is gambling disorder. This modification, however, is of great symbolic significance: it clearly represents the shift towards a new perspective in which the presence of a psychoactive substance is not a prerequisite to addictive disorders.

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References

[1] European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), *European Drug Report 2013: Trends and Developments*, European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Lisbon, Portugal, 2013.

[2] O. Corazza, S. Assi, P. Simonato et al., "Promoting innovation and excellence to face the rapid diffusion of novel Psychoactive substances in the EU: the outcomes of the reDNet project," *Human Psychopharmacology*, vol. 28, no. 4, pp. 317–323, 2013.

[3] O. Corazza, Z. Demetrovics, W. van den Brink, and F. Schifano, "'Legal highs' an inappropriate term for 'Novel Psychoactive Drugs' in drug prevention and scientific debate," *International Journal of Drug Policy*, vol. 24, no. 1, pp. 82–83, 2013.

[4] F. Schifano, P. Deluca, L. Agosti et al., "New trends in the cyber and street market of recreational drugs? The case of 2C-T-7 ("Blue Mystic")," *Journal of Psychopharmacology*, vol. 19, no. 6, pp. 675–679, 2005.

[5] F. Schifano, M. Leoni, G. Martinotti, S. Rawaf, and F. Rovetto, "Importance of cyberspace for the assessment of the drug abuse market: preliminary results from the Psychonaut 2002 project," *Cyberpsychology and Behavior*, vol. 6, no. 4, pp. 405–410, 2003.

[6] W. R. Eadington, "Measuring costs from permitted gaming: concepts and categories in evaluating gambling's consequences," *Journal of Gambling Studies*, vol. 19, no. 2, pp. 185–213, 2003.

[7] G. Martinotti, S. Andreoli, E. Giametta, V. Poli, P. Bria, and L. Janiri, "The dimensional assessment of personality in pathologic and social gamblers: the role of novelty seeking and self-transcendence," *Comprehensive Psychiatry*, vol. 47, no. 5, pp. 350–356, 2006.

[8] S. Achab, L. Karila, and Y. Khazaal, "Pathological gambling: update on decision making and neuro-functional studies in clinical samples," *Current Pharmaceutical Design*, vol. 20, no. 25, pp. 4000–4011, 2014.

[9] J. E. Grant, M. N. Potenza, A. Weinstein, and D. A. Gorelick, "Introduction to behavioral addictions," *The American Journal of Drug and Alcohol Abuse*, vol. 36, no. 5, pp. 233–241, 2010.

[10] Z. Demetrovics and M. D. Griffiths, "Behavioral addictions: past, present and future," *Journal of Behavioral Addictions*, vol. 1, no. 1, pp. 1–2, 2012.

[11] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Association, Washington, DC, USA, 5th edition, 2013.

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Research Article

Substance Use in the Club Scene of Rome: A Pilot Study

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Objective. Over the last few years, a wide number of unregulated substances have been marketed on the Web and in smart and head shops; they are usually advertised as legal alternatives to commonly known drugs and are defined as "smart drugs," "legal highs," and "novel psychoactive substances" (NPS). Aim of our work is to describe use habits and distribution of NPS in a population of young adults in Rome club scene. *Methods*. A self-administered questionnaire was proposed to subjects over 18 years of age at the entrance of 5 nightclubs in Rome. Socioeconomic characteristics and substance use were investigated. *Results*. Preliminary results give evidence that 78% of respondents have a lifetime history of NPS use. In addition, 56% of the sample has consumed illicit drugs in the past and 39% has used psychoactive substances in the 12 hours preceding the questionnaire administration. *Conclusions*. A significant proportion of subjects report use of novel psychoactive substances; traditional illicit drugs consumption, particularly cocaine, appears to be very high as well in the club scene. These data highlight a serious public health challenge, since pharmacological, toxicological, and psychopathological effects linked to interactions among all these substances may be unpredictable and sometimes fatal in vulnerable individuals.

1. Introduction

So-called "club drugs," psychoactive substances associated with club and rave cultures, proliferated in the 1990s and remained key substances for years among youth and young adults [1]. The U.S. National Institute on Drug Abuse (NIDA) in its "Community Alert on Club Drugs" identified ecstasy (3,4-methylenedioxymethamphetamine or MDMA), Gamma-hydroxybutyrate (GHB), ketamine, Rohypnol (flunitrazepam), methamphetamine, and lysergic acid diethylamide (LSD) as "club drugs" [2], while the U.S. Office of National Drug Control Policy described only four specific club drugs: MDMA, GHB, ketamine, and Rohypnol [3].

Epidemiological studies have shown that factors associated with recreational nightlife activities, such as music preference and choice of the venue, may be considered as relevant predictors of illegal drug use in several European countries [4]. Similarly, in the US, Moore and Miles have found an association between substance use and alternative music styles in the electronic music scene [5].

It is becoming increasingly clear that the drugs used in clubs are heterogeneous and ever-changing [6]; moreover, during the last few years, a wide number of unregulated natural and synthetic New Psychoactive Substances (NPS) have made their appearance on the market [7].

NPS are drugs of abuse, either in a pure form or in a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but that may pose a serious public health threat. In this context, the term "new" does not

necessarily refer to newly synthesized molecules, but mainly to substances that have recently become available [7]. Many of these substances were, in fact, firstly synthesized and patented in the 1970s or even earlier, but only recently their chemistry or process of synthesis has been slightly modified to produce effects similar to known illicit substances. On the basis of the above-mentioned definition, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the European Police Office identified the following groups of substances, covered by the Early Warning System on NPS [8]:

(i) *phenethylamines*, which encompass a wide range of substances that may exhibit stimulant, entactogenic, or hallucinogenic effects;

(ii) *tryptamines*, which include a number of substances that have predominantly hallucinogenic effects;

(iii) *piperazines*, represented, inter alia, by m-chlorophenylpiperazine (mCPP) and BZP, both of which are central nervous system stimulants;

(iv) *synthetic cathinones*, which have stimulant effects; the main cathinone derivatives are the semisynthetic methcathinone and the synthetic compounds mephedrone, methylone, and methylenedioxypyrovalerone (MDPV);

(v) *synthetic cannabinoids*, which are functionally similar to Δ9-tetrahydrocannabinol (THC), the active compound of cannabis.

Other substances reported by the Early Warning System include various plant-derived and synthetic psychoactive substances (e.g., indanes, benzodifuranyls, narcotic analgesics, synthetic cocaine derivatives, ketamine and phencyclidine derivatives), which do not strictly belong to any of the previously mentioned drug groups. A number of medicinal products and derivatives are also included [9].

NPS are rapidly appearing in more and more sophisticated forms and often remain unregulated for a long period [7]. EMCDDA stated that, in 2012, 280 potentially harmful "legal highs" have been produced in Europe alone [8]. These substances are often synthesized in underground laboratories, simply modifying the molecular structure of controlled drugs, hence raising concerns related to the potential presence of contaminating agents [10]. The significant informational, promotional, and distributional capacity of the Internet plays an important role in the NPS market: global web-based marketing and distribution, distinct from illegal street markets, have developed in the past years [9]. The number of online shops providing customers with NPS in European Union countries has increased from 170 in January 2010 to 314 in January 2011, and 693 in January 2012 [8]. The Internet offers many advantages to NPS suppliers, as it allows access to a vast number of potential users, and suppliers do not need large upfront investments and can retain some level of anonymity. In addition, suppliers may be able to bypass the laws of different countries, thus making enforcement or legal action in response to their activities very difficult. It is also important to point out that, in many cases, sellers fail to list ingredients, side effects, and drug interactions of the advertised products [7]. Moreover, the Internet serves as a repository of information for several groups of people. Drug users can obtain information through online forums, chat rooms, and blogs and find out about new products. They can also share with other users their experiences and the effects of the substances, as well as the recommended sources and ways of delivery [10]. The possibility of purchasing NPS from websites makes these drugs easily available to vulnerable individuals, including children and adolescents. These subjects may also be encouraged by diffuse online comments/messages/videos related to NPS intake experiences. This may be an issue of concern, if one considers that an estimated 61% of young Europeans aged between 15 and 24 years typically quote the Internet as a potential source of information on illicit drugs [11]. Moreover, the current legal status of a number of NPS may arguably facilitate increasing levels of popularity of these drugs and may affect as well the users' perception of risks associated with their consumption. The idea that legality can equate with safety still remains well grounded amongst some recreational users [12].

The limited information available suggests that NPS spread at a global level is far from negligible, and, excluding cannabis from the analysis, it comes close to, or even exceeds, the spread of several controlled drugs. NPS have been reported in many countries in recent years. What is actually known today, however, maybe just the very tip of the iceberg, as systematic studies on the diffusion of NPS do not exist [9], except for single substances [13, 14].

The consumption of NPS in Italy in 2011 was estimated to be about 1%, placing the country 27th out of 28 European countries in the ranking of NPS use [14]. In the last years, the Italian Department of Drug Control has promoted the development of a concise update on the main features of identified NPS, developing as well a series of strategic guidelines, objectives, and actions in order to begin constructing a response to tackle this emerging issue [15]. Although the Italian data are encouraging and show the effectiveness of the countermeasures taken to deal with this new phenomenon (e.g., to contrast NPS sale in smart shops and sex shops), the presence of toxic products still new on the market remains an open issue to which great attention is paid. Moreover, while estimates on general population are essential to better illustrate drug trends, it is also important to identify and assess consumption prevalence among key groups and target populations.

Aim of our study was to describe use habits and distribution of NPS and other substances in a population of young adults. Considering that surveys undertaken in nightclubs and other nighttime economy venues are a good source of data in order to assess the use of recreational drugs in a high-prevalence use population [16], we selected a sample of young adults involved in Rome nightclub scene, investigating substance use as well as possible psychotropic and side effects.

2. Methods

2.1. Study Participants. A questionnaire on recreational substances misuse has been proposed between September and

November 2013 to a population sample (18–30 years old) in 5 nightclubs in Rome. Potential study participants were approached by a member of the research team at the entrance or in the smoking/chill-out area inside the clubs. The self-administered questionnaire was collected in anonymous way by our team of psychologists and psychiatrists, with the support of a peer group working.

In the first part, the questionnaire included socioeconomic characteristics (age, gender, job status, lifestyle) and perceived mental stress. Written informed consent was systematically obtained for every subject, according to the Declaration of Helsinki.

2.2. Previous Illicit Drugs Use. Study participants were asked whether they had used, in the past, any illicit drug among heroin (diacetylmorphine) and other opiates (opium, morphine, codeine, heroin, fentanyl, methadone, meperidine, L-alpha-acetylmethadol [LAAM]), cannabis (marijuana, hashish), cocaine and derivatives (e.g., crack), amphetamines, methamphetamine, hallucinogens (lysergic acid diethylamide [LSD], mescaline, psilocybin), and stimulatory hallucinogens (MDMA [ecstasy], phencyclidine [PCP]). Common street names of illicit drugs, both single and in combination (e.g., speed, speedball, spaceball), were also listed. For illicit drugs with multiple routes of administration (ROA), interviewees were asked to specify the ROA and pharmaceutical form (e.g., powder, pill, dust).

Moreover, study participants were asked if they had ever abused alcohol (according to the DSM IV-TR criteria) with the above-mentioned illicit drugs and, in case of positive response, they were asked to specify which drugs and the frequency of this behavior.

2.3. Previous Use of Novel Psychoactive Substances and/or Clubs Drugs. Study participants were asked whether they had used a NPS and/or a club drug in the past. Listed substances included synthetic cannabinoids, Gamma-hydroxybutyrate (GHB), mephedrone, ketamine, *Salvia divinorum*, amyl nitrite, and psilocybin. Common street or on-line names of NPS (e.g., poppers, liquid ecstasy, liquid X, magic mushrooms) were included among the questionnaire options as well. If the participants answered positively, they were asked to specify if the chosen substance was a powder, a pill, or another type of NPS.

2.4. Current Use of Psychoactive Substances and Alcohol. Study participants were asked to indicate whether they had used psychoactive substances in the 12 hours preceding the questionnaire administration. If the answer was positive, they were asked to specify if they had assumed also alcohol as well.

2.5. Data Analysis. Data are reported as means, standard deviation, and percentages where appropriate. Statistical comparison of the proportions of those reporting use on the night of the survey was undertaken by Chi-square (χ^2). SPSS version 14.0 was used for all analyses.

Table 1

Novel psychoactive substance/club drugs	Lifetime use (% values of the whole sample)	Absolute values
Synthetic cannabinoid	35	96
Gamma-hydroxybutyrate (GHB)	10.2	28
Mephedrone	18.8	51
Ketamine	18	49
Salvia divinorum	3.2	9
Amyl nitrite (poppers)	45	123
Lysergic acid diethylamide (LSD)	24	66
Psilocybin	4	11

3. Results

3.1. Participant Characteristics. This sample was composed of 273 subjects. Regarding the sociodemographic characteristics, mean age of participants was 25.4 years, 53% were males and 47% females, and all were residents in the municipality of Rome. 62% of subjects lived with parents, 13% alone and the remaining 25% with other people. With regard to employment status, 27% declared to have a job, 46% were students, 10% were working students, and, finally, 17% were unemployed.

3.2. Previous Illicit Drugs Use. The prevalence of lifetime previous illicit drugs use was 56% (*n*. 153), and 48% of the subjects claimed to have consumed alcohol together with illegal psychoactive substances at least once.

3.3. Previous Use of Novel Psychoactive Substances and/or Clubs Drugs. Surprisingly, 78% of respondents declared a lifetime previous use of NPS/club drugs, such as amyl nitrite (45%), synthetic cannabinoids (35%), lysergic acid diethylamide (LSD) (24%), mephedrone (18.8%), ketamine (18%), Gamma-hydroxybutyrate (GHB) (10.2%), psilocybin (4%), and *Salvia divinorum* (3.2%) (see Table 1).

3.4. Current Use of Psychoactive Substances and Alcohol. At the time of the questionnaire administration, 39% of the sample (*n*. 106) claimed to have assumed psychoactive substances in the previous 12 hours. Among the most prevalent substances, the percentages were distributed as listed: cocaine 89% (*n*. 94), cannabis 20% (*n*. 21), ketamine 11% (*n*. 12), ecstasy 10% (*n*. 11), methamphetamine 5% (*n*. 6). Other psychoactive substances had a prevalence of use of less than 1% (*n*. 1) (see Figure 1). Overall, on the night of the survey, cocaine had a prevalence higher than cannabis ($P < 0.001$), ketamine ($P < 0.001$), ecstasy ($P < 0.001$), or methamphetamine ($P < 0.001$).

Moreover, the sample showed high polydrug use frequencies: among psychoactive substances consumers, the totality (100%) claimed a concurrent alcohol consumption, and 31%

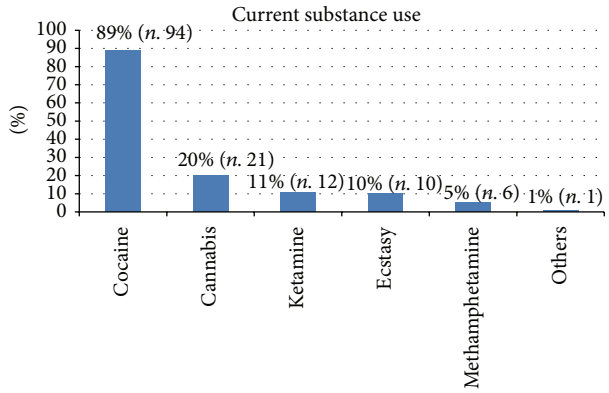

Figure 1: Percentages of substance use within the group of current users.

(12% of the total sample) (*n*. 33) claimed the assumption of two or more illicit drugs.

4. Discussion

In the surveyed sample, a significant fraction (78%) reported a previous lifetime history of use of one or more NPS ("legal high") and/or club drugs. The lifetime use of amyl nitrite was particularly high, probably for its easy availability and its sexual enhancing properties [17]. However, the use of newer psychoactive substances was also very high (see Table 1 for details). There are two main possible ways to explain this finding: (1) a recent spread of knowledge and consumption of NPS in the Italian youth population or (2) despite an overall limited use, a widespread consumption in peculiar subpopulations. However, notwithstanding this impressive datum, there was no evidence of recent use (on the night of the survey) for new psychoactive substances. On the contrary, a very high consumption was highlighted for cocaine, followed by cannabis and other substances commonly rubricated as "club drugs" (ketamine, ecstasy, methamphetamine) [2, 3]. These results contrast with other studies on the recreational drug scene in the UK, which reported a fairly significant consumption of mephedrone [18–20], Gamma-butyrolactone (GBL) [21], and amyl nitrite [20]. Our results are more similar to reports on the nightlife scenes of US [22] and continental Europe [23]. Cocaine is easily available and in recent years has become cheaper than in the past [24]: these reasons can help to explain its high prevalence of use.

Our results evidence high rates of polydrug use in the subpopulation of nightclubs attendees. This could determine a serious public health challenge, since pharmacological, toxicological, and psychopathological effects due to interactions between these substances may be unpredictable and fatal as well in vulnerable individuals. As previously stated, very few pharmacological/toxicological data are available in the peer-reviewed scientific literature, with the limited knowledge being mostly restricted to preclinical studies. Moreover, a polydrug use may lead to deep neurobiochemical central nervous system alterations, which may make these individuals extremely difficult to be pharmacologically treated, even by expert mental health professionals.

Club drugs have also an important social impact in terms of crimes and violence [25], and they may contribute to the global burden of diseases, together with mental disorders and traditional illicit drugs (e.g., heroin) [26]. In 2010, illicit drug dependence accounted for 20 million DALYs (disability-adjusted life years), being responsible for 0,8% (0.6–1.0) of global all-cause DALYs [27]. At present, however, the overall dependence liability of these substances seems lower than that of heroin and amphetamines [27].

5. Limitations

This is a pilot study with a small sample size: for definitive conclusions it is necessary to expand the sample. However, our sample size is comparable with that considered in other in situ nighttime economy surveys [28]. Increasing the available data would allow having greater statistical significance, also in order to identify drugs complications and interactions, to verify the indirect effects of substances on the social and working capacity and, maybe, to evaluate the consequences of their long-term assumption. An intrinsic limitation is that drugs abuse in club scene appears to be jeopardized, and it is difficult to extend the results obtained at a venue to other venues or countries. Another limitation is that subjects may not be aware of what drug(s) they had actually used; however every effort was made in the attempt to be accurate (e.g., use of substances street names, specification of formulation and route of administration).

6. Conclusions

This survey has shown that although a significant proportion of individuals report a lifetime use of NPS, these drugs have little significance in the recreational drugs scene. Therefore, to investigate the recreational drugs scene might not be the better strategy to monitor the extent of NPS consumption in the European Union and elsewhere. However, multicenter large-scale studies need to be carried out. Again, it is here suggested that better international collaboration levels are needed to tackle the new and fast growing phenomenon of NPS availability from the web and other channels of supply.

Regarding traditional illicit drugs, cocaine misuse is very high in club culture, significantly higher than substances usually identified as club drugs (MDMA, ketamine, methamphetamine). Moreover, health and other professionals should be accurately informed about the trend of misuse of multiple psychoactive substances in association with alcohol.

Further studies are needed to design better intervention strategies in subjects with problematic recreational drugs use within the nightclub environment.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] E. S. Rome, "It's a rave new world: rave culture and illicit drug use in the young," *Cleveland Clinic Journal of Medicine*, vol. 68, no. 6, pp. 541–550, 2001.

[2] National Institute on Drug Abuse, Community drug alert bulletin—"club drugs", 1999.

[3] Office of National Drug Control Policy, 2004.

[4] A. Calafat, C. Fernández, M. Juan, and E. Becoña, "Recreational nightlife: risk and protective factors for drug misuse among young Europeans in recreational environments," *Drugs: Education, Prevention and Policy*, vol. 15, no. 2, pp. 189–200, 2008.

[5] K. Moore and S. Miles, "Young people, dance and the subcultural consumption of drugs," *Addiction Research and Theory*, vol. 12, no. 6, pp. 507–523, 2004.

[6] P. Tellier, "Club drugs: is it all ecstasy?" *Pediatric Annals*, vol. 31, no. 9, pp. 550–556, 2002.

[7] United Nations Office on Drugs and Crime (UNODC), *New Psychoactive Substances Report*, A Report from the Global SMART Programme, 2013.

[8] European Monitoring Centre for Drugs and Drug Addiction, *Annual Report 2012: The State of the Drugs Problem in Europe*, Publications Office of the European Union, Luxembourg, Luxembourg, 2012.

[9] United Nations Office on Drugs and Crime (UNODC), http://www.unodc.org/unodc/secured/wdr/wdr2013/World_Drug_Report_2013.pdf.

[10] O. Corazza, S. Assi, P. Simonato et al., "Promoting innovation and excellence to face the rapid diffusion of novel Psychoactive substances in the EU: the outcomes of the reDNet project," *Human Psychopharmacology*, vol. 28, no. 4, pp. 317–323, 2013.

[11] O. Corazza, F. Schifano, P. Simonato et al., "Phenomenon of new drugs on the internet: the case of ketamine derivative methoxetamine," *Human Psychopharmacology*, vol. 27, no. 2, pp. 145–149, 2012.

[12] F. Schifano, J. Corkery, A. Oyefeso, T. Tonia, and A. H. Ghodse, "Trapped in the "K-hole": overview of deaths associated with ketamine misuse in the UK (1993–2006)," *Journal of Clinical Psychopharmacology*, vol. 28, no. 1, pp. 114–116, 2008.

[13] A. R. Winstock, S. Kaar, and R. Borschmann, "Dimethyltryptamine (DMT): prevalence, user characteristics and abuse liability in a large global sample," *Journal of Psychopharmacology*, vol. 28, no. 1, pp. 49–54, 2014.

[14] F. Schifano, P. Deluca, L. Agosti et al., "New trends in the cyber and street market of recreational drugs? The case of 2C-T-7 ('Blue Mystic')," *Journal of Psychopharmacology*, vol. 19, no. 6, pp. 675–679, 2005.

[15] Italian Department of Drug Control and Office of the Prime Minister, National Action Plan 2010–2013 Drug Control, October 22, 2010.

[16] D. M. Wood, M. Nicolaou, and P. I. Dargan, "Epidemiology of recreational drug toxicity in a nightclub environment," *Substance Use & Misuse*, vol. 44, no. 11, pp. 1495–1502, 2009.

[17] T. Lea, G. Prestage, L. Mao, I. Zablotska, J. de Wit, and M. Holt, "Trends in drug use among gay and bisexual men in Sydney, Melbourne and Queensland, Australia," *Drug and Alcohol Review*, vol. 32, no. 1, pp. 39–46, 2013.

[18] A. Winstock, "Drugs survey," *MixMag*, vol. 238, pp. 49–59, 2011.

[19] D. M. Wood, L. Hunter, F. Measham, and P. I. Dargan, "Limited use of novel psychoactive substances in South London nightclubs," *QJM*, vol. 105, no. 10, Article ID hcs107, pp. 959–964, 2012.

[20] K. Moore, P. I. Dargan, D. M. Wood, and F. Measham, "Do novel psychoactive substances displace established club drugs, supplement them or act as drugs of initiation? The relationship between mephedrone , ecstasy and cocaine," *European Addiction Research*, vol. 19, no. 5, pp. 276–282, 2013.

[21] T. Yamamoto, A. Kawsar, J. Ramsey, P.I. Dargan, and D. M. Wood, "Monitoring trends in recreational drug use from the analysis of the contents of amnesty bins in gay dance clubs," *Oxford Journals Medicine*, vol. 106, no. 12, pp. 1111–1117, 2013.

[22] D. E. Ramo, C. Grov, K. Delucchi, B. C. Kelly, and J. T. Parsons, "Typology of club drug use among young adults recruited using time-space sampling," *Drug and Alcohol Dependence*, vol. 107, no. 2-3, pp. 119–127, 2010.

[23] T. van Havere, W. Vanderplasschen, J. Lammertyn, E. Broekaert, and M. Bellis, "Drug use and nightlife: more than just dance music," *Substance Abuse: Treatment, Prevention, and Policy*, vol. 6, no. 1, article 18, 2011.

[24] K. Moore, P. I. Dargan, D. M. Wood, and F. Measham, "Do novel psychoactive substances displace established club drugs, supplement them or act as drugs of initiation? The relationship between mephedrone, ecstasy and cocaine," *European Addiction Research*, vol. 19, no. 5, pp. 276–282, 2013.

[25] L. P. Carter, "Potential impact of drug effects, availability, pharmacokinetics, and screening on estimates of drugs implicated in cases of assault," *Drug Testing and Analysis*, vol. 3, no. 9, pp. 586–593, 2011.

[26] M. T. Lynskey and J. Strang, "The global burden of drug use and mental disorders," *The Lancet*, vol. 382, no. 9940, pp. 1540–1542, 2013.

[27] L. Degenhardt, H. A. Whiteford, A. J. Ferrari et al., "Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010," *The Lancet*, vol. 382, no. 9904, pp. 1564–1574, 2013.

[28] F. Measham, K. Moore, and Ø. J. Mephedrone, "'Bubble' and unidentified white powders: the contested identities of synthetic 'legal highs'," *Drugs and Alcohol Today*, vol. 3, pp. 137–146, 2011.

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Research Article

Early Detection of Pathological Gambling: Betting on GPs' Beliefs and Attitudes

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Pathological gambling (PG) is an addictive disorder with harm related to the high psychiatric comorbidity and increased suicidal risk. Prevalence rates in general population range from 0.2% to 2.1%. Problem gamblers are hard to attract to treatment programs for several proper reasons and for obstacles (e.g., accessibility). To address these obstacles, primary care (where the problem gambling (PrG) prevalence seems to be 6.2%) has a crucial role to play (i.e., identifying and referring patients to specialized treatment programs and treating at first line when needed and possible) in the era of online gambling offer expansion. The present work aimed to collect data on resources in the field from GPs themselves, using a 24-item online questionnaire. Swiss French-speaking participants were asked about their screening practice and knowledge. The results state that the vast majority of them are aware of the existence and the potential impact of PrG on their patients. However, PrG screening is not systematic and their knowledge of adequate treatments or referral methods is scarce. GPs being central to health screening in general, targeted advice and training on short screening tools and better knowledge of referral pathways should be promoted and continued to empower the GP's management skills in a public health approach.

1. Introduction

Pathological gambling (PG) has been recently added as a gambling disorder to the substance-related disorders chapter of DSM 5 [1], as a result of the empiric findings provided by the research literature supporting its similarity with substance use disorders (SUD). Indeed, it has been shown that PG shares clinical expression, comorbidity, neurobiological mechanisms [2–5], and treatment options [6–8] with SUD and reward-related behaviors.

PG harm related to its high psychiatric comorbidity, mostly substance use disorders [9] and increased suicidal risk [10]. Vulnerable subgroup populations such as adolescents are also affected by gambling disorders [11]. Prevalence rates in the general population range are ranging from 0.2% to 2.1% [12–14] for pathological gamblers and from 0.6% to 5.5% for problem gamblers [13, 15–18]. The prevalence seems to be more important (6.2%) in primary care services [19]. Problem gamblers are hard to attract to treatment programs, partly due to their feelings of shame and denial [20]. Only 0.4% to 3% of them seek help for their difficulties [21, 22] and a five-year latent period is observed between the first symptomatic presentation and the first attempt to seek care [23]. Hence, general practitioners (GPs) as primary care providers have a crucial role to play in the early detection and intervention on problem gambling (PrG) [24, 25]. There is a paucity of studies on the PrG management resources and screening practices of GPs. Fourteen years ago, in Canada, a structured national plan was designed to evolve physicians in PrG management [26]. The needs (PrG resources available and awareness on their existence) were studied in a sample of 54 physicians from the 800 contacted. Results showed a low awareness on PrG resources that have been considered by participants insufficient to fulfill the needs [26]. Concern about the lack of knowledge, education, and training in PrG and its perception as a nonmedical problem but rather as a character defect was raised as challenges and obstacles to GPs' evolvement in PrG management [26]. An Australian paper [24] presented the way GPs can help in early detection and intervention and reported a pilot project that provided resources to GPs.

Table 1: Sociodemographic data.

Total sample ($N = 71$)	
Age (years), median (min–max)	53 (34–71)
Gender, *n* (%)	
Female	25 (35.2)
Male	43 (60.6)
Missing	3 (4.2)
Practice duration (years), median (min–max)	17 (1–38)
Medical specialization, *n* (%)	
General practitioner	33 (46.5)
Internist	33 (46.5)
General practitioner and internist	1 (1.4)
Internist and other	3 (4.2)
No specialization	1 (1.4)
Area of practice, *n* (%)	
Fribourg	1 (1.4)
Geneva	31 (43.7)
Jura	0 (0)
Neuchâtel	23 (32.4)
Valais	0 (0)
Vaud	16 (22.5)

Table 2: Participants beliefs on excessive gambling.

Total sample ($N = 71$)	*n* (%)
In your opinion, excessive gambling in Swiss French-speaking area is	
Not an issue	0 (0)
A minor issue	18 (25.4)
A major issue	41 (57.7)
A very major issue	3 (4.2)
I do not know	9 (12.7)
Your interest in excessive gambling and gamblers' indebtedness is	
Important	11 (15.5)
Medium	38 (53.5)
Low	18 (25.4)
Null	2 (2.8)
I do not know	2 (2.8)
Do you think gambling could become excessive or addictive	
Total agreement	66 (93.0)
Partial agreement	4 (5.6)
Partial disagreement	0 (0)
Total disagreement	0 (0)
I do not know	1 (1.4)
Do you think gambling could lead to indebtedness	
Total agreement	69 (97.2)
Partial agreement	2 (2.8)
Partial disagreement	0 (0)
Total disagreement	0 (0)
I do not know	0 (0)
Does excessive gambling worsen indebtedness in the current economical context	
Total agreement	45 (63.4)
Partial agreement	18 (25.4)
Partial disagreement	2 (2.8)
Total disagreement	0 (0)
I do not know	5 (7.0)
Missing	1 (1.4)

Results from the 24 GPs (with referral experience in PrG) from the 51 that received information and material on PrG (e.g., importance, list of referral services, and simple advice on the way to assist patients). The majority of participants were convinced of the role they can play in PrG management [24]. However, lack of knowledge was reported by almost half of the sample (even if they had referral experience in the field) and a difficulty to ask patients "out of the blue" if they gamble [24].

Another awareness study of PrG in 180 health care providers (nurses, physicians, and social workers) [27] showed that the vast majority are aware of the existence of PrG but only a minority are effectively screening their patients.

Screening for health problems in care providers themselves is not a frequent question. Regarding PG, a prevalence rate in American general practitioners of 5% has been reported [28].

This study aims first to evaluate interest and knowledge of GPs regarding PrG and the way they deal with it in their daily clinical practice. Secondly, it aims to screen for PrG in GPs themselves.

2. Methods

2.1. Sample. Swiss GPs with a medical practice in the 6 French-speaking areas (FSAs) of Switzerland were invited to participate anonymously in an online survey.

Participants were recruited between March and May 2011 via their physician's regional association through an e-mail informing about the study's aims. The participants were directed through a web link to the questionnaire.

2.2. Measures. A 24-item online questionnaire was developed for the study on Survey Monkey software. After sociodemographic data (Table 1), five items investigated participants' beliefs on PrG (Table 2). Then, participants were asked about their PrG screening practice (Table 3). They were presented a text-response item (to avoid oriented responses) to specify the PrG screening tools they use. They were also invited to estimate the rate of PrG and related debts issues in their active pool of patients. Practitioners were then asked how they manage PrG and its financial consequences in their patients (Table 3). The last section of the questionnaire consisted of items on the participants' impression about their knowledge of PrG disorder, on the existing specialized local treatment network, and their estimated need for information

Table 3: Participants attitudes towards excessive gambling.

Total sample ($N = 71$)	n (%)
Do you screen for excessive gambling	
Systematically	0 (0)
Often	5 (7.0)
Rarely	25 (35.2)
Never	22 (31.1)
I do not know	1 (1.4)
Missing	18 (25.4)
Do you screen for indebtedness	
Systematically	1 (1.4)
Often	24 (33.8)
Rarely	24 (33.8)
Never	6 (8.5)
I do not know	2 (2.8)
Missing	14 (19.7)
Your attitude towards excessive gambling is	
I refer to specialist	37 (52.1)
I treat it	5 (7.0)
I do not do anything	2 (2.8)
I do not know	22 (31.8)
Missing	5 (7.0)
Your attitude towards indebtedness is	
I refer to specialist	34 (47.9)
I treat it	15 (21.1)
I do not do nothing	3 (4.2)
I do not know	7 (9.9)
Missing	12 (16.9)
The best management of excessive gamblers is in referral to	
Specialized multidisciplinary centers (doctors, psychologists, and social workers)	57 (80.3)
Private psychiatrists	2 (2.8)
General practitioners	3 (4.2)
Social services	1 (1.4)
Other	3 (4.2)
I do not know	2 (2.8)
Missing	3 (4.2)

Table 4: Self-reported knowledge of problem gambling.

Total sample ($N = 71$)	n (%)
My knowledge of problem gambling is	
Very satisfying	0 (0)
Satisfying	12 (16.9)
Dissatisfying	46 (64.8)
Null	10 (14.1)
I do not know	0 (0)
Missing	3 (4.2)
My knowledge of problem gambling care network is	
Very satisfying	0 (0)
Satisfying	15 (21.1)
Dissatisfying	32 (45.1)
Null	18 (25.4)
I do not know	3 (4.2)
Missing	3 (4.2)
I desire more information about problem gambling	
Total agreement	39 (54.9)
Partial agreement	22 (31.0)
Partial disagreement	3 (4.2)
Total disagreement	2 (2.8)
I do not know	1 (1.4)
Missing	4 (5.6)
I desire more training on problem gambling	
Total agreement	19 (26.8)
Partial agreement	36 (50.7)
Partial disagreement	6 (8.5)
Total disagreement	3 (4.2)
I do not know	1 (1.4)
Missing	6 (8.5)

Table 5: Screening for PrG in participants.

Total sample ($N = 71$)	n (%)
Have you ever felt the need to bet more and more money	
Yes	1 (1.4)
No	67 (94.4)
I do not know	0 (0)
Missing	3 (4.2)
Have you ever had to lie to people important to you about how much you gambled	
Yes	0 (0)
No	68 (95.8)
I do not know	0 (0)
Missing	3 (4.2)

and training (Table 4). At the end of the questionnaire, responders were themselves screened for PrG, using the 2-item Lie-bet test [29] "*Have you ever felt the need to bet more and more money?*" and *"Have you ever had to lie to people important to you about how much you gambled?*" (Table 5).

2.3. Statistical Analysis. SPSS 18.0 (Statistical Package for the Social Sciences, IBM Inc., Chicago) software program was used to perform the statistical analyses. First, descriptive statistics were computed for the participants' characteristics (demographics and beliefs representation) and reported as medians, ranges, and percentages. For the sake of completeness, missing data are also provided in the tables.

Next, we looked for associations between screening frequency and GPs' interest in PrG, between knowledge of

PrG, respectively, knowledge of PrG network, and screening practice for PrG, and finally between the need for information/training on PrG and knowledge of the topic, using the Pearson chi-square tests. When the expected frequency criteria were not met due to small cell sample size, adjacent categories were collapsed into smaller categories, where appropriate, in order to fulfill the necessary Pearson chi-square requirements and to gain statistical power. Two-by-two tables that did not meet these requirements were analyzed by the Fisher exact tests. Hence, for instance, knowledge of the topic reduces to two categories: very satisfactory/satisfactory versus insufficient/no knowledge. The same is the case for screening for excessive gambling frequency (systematically/often versus rarely/never) and demand for more information and training (total agreement/partial agreement versus partial disagreement/total disagreement).

3. Results and Discussion

The survey was relatively well received by Swiss GPs' professional associations in the French speaking area with 66% of acceptance to relay the information and the link to the online questionnaire. The sample consisted of 71 GPs accepting to participate in the survey. A majority of them (95.8%) filled out the questionnaires. Respondents were mostly men (63.2%), with a median age of 53 years and a median practice experience of 17 years as GP (Table 1). The vast majority is qualified specialists in primary care (general practitioner and/or internist) and their area of practice is given in Table 1.

When GPs were asked to estimate PrG rate in their active pool of patients, more than half of them did not answer and 11% declared not knowing this rate, while 24% of them estimated this rate (between 1 and 30%).

3.1. GPs' Beliefs on PrG and Financial Debts. The great majority (99%) expressly recognized believing in the potential addictive properties of gambling and 69% of them showed a keen interest in PrG with all the subsequent financial harm (Table 2). Two-thirds of them (62%) characterized PrG as an important or very important issue of concern in the French-speaking area of Switzerland. The whole sample agreed that gambling could lead to indebtedness and 89% agreed with the worsening of indebtedness related to excessive gambling.

3.2. GPs' Attitudes towards PrG. In their daily practice, while debts were often or systematically screened by 35% of the practitioners, PrG was screened only by a minority (7%) of them (Table 3). Screening habits were during general history taking or PrG being discovered by chance with the occurrence of payment difficulties. There was no relationship found between screening frequency and GPs interest in it ($P = 1$). Investigating PrG management, 52% of GPs referred their patients to a specialist and 7% treated it themselves, while 32% stated they do not know what to do with these problematic patients and 3% do not address this issue at all (Table 3). GPs promote a specialized approach to PrG treatment, in multidisciplinary centers (80%) and by private psychiatrists (3%). In debt management, GPs seemed to be more active than for PrG, with a greater rate of them treating it themselves (21%) and a lesser rate of "I do not know" (10%) responses.

3.3. Self-Reported Knowledge of PrG. Participants estimated their knowledge of PrG and on specialized care network as being null (resp., 14% and 25%) or unsatisfying (resp., 65% and 45%) (Table 4). This was found to be independent of their screening practice for problem gambling (resp., $P = 0.2$ and $P = 0.1$). The majority of participants reported a need for information (86%) and for training (77.5%) on PrG (Table 4). This need was found to be independent of how satisfied they felt about their feeling as satisfied or not from their knowledge of the topic ($P = 0.5$).

One participant screened himself positive for problem gambling according to Lie-bet items [29].

In summary, data showed that the majority of GPs considered gambling addictive and they believed in the importance of problem gambling in their area of practice, estimating furthermore a high rate of PrG and related indebtedness in their own patients. These results are different from those of the Canadian sample of physicians in 2000 [26] but similar to those from the Australian data in 2007 [24]. This highlights the possible mentality changes this last decade regarding PrG status as a medical disorder and constitutes a better chance for GPs to be motivated to play a role in its management. Nevertheless, screening practice was very low and PrG was often discovered by chance when patients experienced financial issues. In addition, GPs interested in PrG did not differ significantly in screening from those who declared less or no interest in the field. This could be explained by the gap between beliefs and attitudes in a real practice setting. Even if GPs believe and take interest in PrG, they probably tend to prioritize managing other disorders (i.e., somatic and/or with short- or medium-term vital risk). They could also feel a lack of time in their consultation to include questions on PrG [30]. This goes in line with the obstacles stated in recent literature to be facing GPs' evolvement in PrG screening (e.g., "lack of time" and "PrG considered as a new problem having a low incidence") [26]. GPs could interest in PrG but could lack suitable and available resources and knowledge on PrG care management. The economically symptomatic PrG (i.e., patient declaring financial issues or incidents of fee payment issues) could be a sign of alert of the disorder for the practitioner, but unfortunately financial consequences are already present. This aspect could be addressed by renewed information on the vital risk of PrG (e.g., suicidal risk) and the importance of the early detection. GPs should also be trained and continuously trained to use basic and suitable PrG screening tools to detect patients before crisis-driven help seeking. GPs in the present work experienced to be screened for PrG using the Lie-bet items. This could have led to an awareness of an existing short and easy screening tool they can use in their daily practice.

Another contrast between GPs beliefs and attitudes regarding PrG is that even if the majority of GPs knew the best treatment approach as being multidisciplinary, only half of them referred to these kinds of treatment

systems. The poor knowledge reported on the specialized local treatment network could explain these findings. This aspect could be addressed by a wider dissemination, through GPs professional associations, of the current accessible information about PrG local treatment systems. Internet could be an interesting, fast, cost-effective, and easy-to-use vector for such information and training dissemination. Several countries have specific web-based information on PrG including information on the local and national specialized treatment centers (i.e., http://www.sos-jeu.ch/, http://www.jeu-aidereference.qc.ca/, and http://www.problemgamblingguide.com/). One possible intervention by GPs once patients screened could be a brief counseling consisting in the recommendation to their patients to visit such web pages to get information on the disorder and the specialized ways of help they could seek. Several medical associations have developed specific material targeting GPs to help them inform their patients on gambling and how to manage PrG in general practice [24]. Since problem gamblers seem to be more likely to accept help from their general practitioner regarding this disorder [31], pharmacotherapy for PrG [6–8] could be an interesting option as it fits with a general practice setting.

A large number of participants stated themselves (79%) as dissatisfied with their knowledge of the disorder and the referring structures and the large majority of the sample declared needing more information (86%) and training (77.5%) on PrG and its management. This is a need that should be addressed by structured specific training and support strategies. Helplines for GPs and supervisions should be considered in addition to specifically designed training materials and settings (i.e., pregraduate, postgraduate, and continuous training). E-learning and distance supervisions (e.g., through e-mails or videoconferences) are emerging tools to build capacity that demonstrated efficacy in other fields in medicine web-platforms dedicated to map and to inform professionals on the tendencies on some addictive behaviors are currently developing [32–35].

The high rate of missing data concerned electively the second part of the questionnaire based on attitudes and knowledge. Taking into account that most of the participants answered to the beliefs, this could be explained by social desirability (i.e., difficulty to report the ignorance on a topic).

With the lack of information on the rate of participants from the panel sought (unknown proportion of affiliated doctors in each professional association at the time of the study), the representativeness of the sample here studied is hard to describe. Furthermore, the only data available is the number of 1183 of Swiss doctors (including GPs) in outpatient sector of the geographic areas concerned by our survey [26, 27, 36]. Another limitation of this work is the predictable lack of statistical significance in the associations testing between beliefs and attitudes due to the small sample size and the missing data. However, descriptive data is the most important contribution of our work. Validity of our results can be appreciated by some indirect indicators. Firstly, data on GPs' attitudes of PrG screening and knowledge are in line with previous studies [24]. Secondly, the proportion of probable PrG in the sample itself (1.5%) was situated in the range of the general Swiss population prevalence [15, 17]. Finally, even if the sample is moderate, a wide age range (34–70 years old) of GPs was represented. Participants, having done their medical studies at different periods in time, represent the panel of different considerations of the PrG as a disorder for the medical community in the last decades.

To our knowledge, this is the first study specifically targeting GPs (regardless to their PrG referral experience) to investigate their beliefs, resources, and practice related to PrG, above all, in the era of an expanding offer of online gambling.

4. Conclusion

The results state that the vast majority of Swiss GPs that participated in the study are aware of the existence and the potential impact of PrG on their patients. But, as expected, the screening of PrG is not systematic and their knowledge of adequate treatments or referral methods is scarce. The discrepancy between beliefs in the harm related to PrG and the lack of its management could be addressed by information, training, and support for general practitioner. The implementation and success of such plan will be facilitated as GPs specifically stated this need. GPs being central to health screening in general and the pressure on them to screen almost all health issues, targeted advice and training (e.g., short screening tools, better knowledge of when to refer to a specialist, and effective pharmacotherapy strategies) should be promoted to empower the GP's management skills in the context of a public health approach. This training and information should be periodically renewed to face new challenges (e.g., Internet as a vector of gambling accessibility but also information and training vector) and to know new management strategies. Our findings can be the first stepping stone in the implementation of such capacity building strategy for PrG early detection and intervention according to the local context. Indeed, concrete tracks can be designed starting from this inventory of representations, knowledge, practice habits, and needs. Such strategy could be inspired by previous afterthoughts [24–26]. This study may have served as a brief intervention to remind the existence and the harms of this disorder. Screening problematic gambling in GPs themselves could have been a novel way to make them aware of possible simple and fast screening tools. The goal of enabling general practitioners is to improve the early detection of problem gamblers and to increase their treatment seeking.

Abbreviations

FSAs: French-speaking areas
GPs: General practitioners
PG: Pathological gambling
PrG: Problem gambling.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

[1] APA, DSM-V, 2013, http://www.dsm5.org/Pages/Default.aspx.

[2] N. M. Petry, C. Blanco, M. Auriacombe et al., "An overview of and rationale for changes proposed for pathological gambling in DSM-5," *Journal of Gambling Studies*, vol. 30, no. 2, pp. 493–502, 2014.

[3] J. H. Baik, "Dopamine signaling in food addiction: role of dopamine D2 receptors," *BMB Reports*, vol. 46, no. 11, pp. 519–526, 2013.

[4] F. Angelucci, G. Martinotti, F. Gelfo et al., "Enhanced BDNF serum levels in patients with severe pathological gambling," *Addiction Biology*, vol. 18, no. 4, pp. 749–751, 2013.

[5] H. Bowden-Jones and L. Clark, "Pathological gambling: a neurobiological and clinical update," *British Journal of Psychiatry*, vol. 199, no. 2, pp. 87–89, 2011.

[6] S. Achab and Y. Khazaal, "Psychopharmacological treatment in pathological gambling: a critical review," *Current Pharmaceutical Design*, vol. 17, no. 14, pp. 1389–1395, 2011.

[7] G. Martinotti, M. Lupi, F. Sarchione et al., "The potential of pregabalin in neurology, psychiatry and addiction: a qualitative overview," *Current Pharmaceutical Design*, vol. 19, no. 35, pp. 6367–6374, 2013.

[8] M. Pettorruso, G. Martinotti, M. di Nicola et al., "Amantadine in the treatment of pathological gambling: a case report," *Frontiers in Psychiatry*, vol. 3, article 102, 2012.

[9] A. Bischof, C. Meyer, G. Bischof, N. Kastirke, U. John, and H. Rumpf, "Comorbid Axis I-disorders among subjects with pathological, problem, or at-risk gambling recruited from the general population in Germany: results of the PAGE study," *Psychiatry Research*, vol. 210, no. 3, pp. 1065–1070, 2013.

[10] N. Thon, U. W. Preuss, A. Pölzleitner et al., "Prevalence of suicide attempts in pathological gamblers in a nationwide Austrian treatment sample," *General Hospital Psychiatry*, vol. 36, no. 3, pp. 342–346, 2014.

[11] C. Villella, G. Martinotti, M. Di Nicola et al., "Behavioural addictions in adolescents and young adults: results from a prevalence study," *Journal of Gambling Studies*, vol. 27, no. 2, pp. 203–214, 2011.

[12] A. G. P. Commission, *Australia's Gambling Industries*, 1999, edited by C. AusInfo.

[13] J. Jonsson and P. Psykologi, "An overview of prevalence surveys of problem and pathological gambling in the Nordic countries," *Journal of Gambling Issues*, vol. 18, pp. 31–38, 2006.

[14] G. Meyer, T. Hayer, and M. Griffiths, Eds., *Problem Gambling in Europe: Challenges, Prevention, and Interventions*, Interscience, New York, NY, USA, 2009.

[15] G. Bondolfi, C. Osiek, and F. Ferrero, "Prevalence estimates of pathological gambling in Switzerland," *Acta Psychiatrica Scandinavica*, vol. 101, no. 6, pp. 473–475, 2000.

[16] J. Welte, G. Barnes, W. Wieczorek, M.-C. Tidwell, and J. Parker, "Alcohol and gambling pathology among U.S. adults: prevalence, demographic patterns and comorbidity," *Journal of Studies on Alcohol*, vol. 62, no. 5, pp. 706–712, 2001.

[17] G. Bondolfi, F. Jermann, F. Ferrero, D. Zullino, and C. H. Osiek, "Prevalence of pathological gambling in Switzerland after the opening of casinos and the introduction of new preventive legislation," *Acta Psychiatrica Scandinavica*, vol. 117, no. 3, pp. 236–239, 2008.

[18] S. Kairouz, L. Nadeau, and C. Paradis, "Portrait du jeu au Québec: prévalence, incidence et trajectoires sur quatre ans," in *Enquête ENHJEU- Québec*, p. 48, Université Concordia, Montréal, Canada, 2011.

[19] A. V. Pasternak IV, "Prevalence of gambling disorders in a primary care setting," *Archives of Family Medicine*, vol. 8, no. 6, pp. 515–520, 1999.

[20] H. Suurvali, J. Cordingley, D. C. Hodgins, and J. Cunningham, "Barriers to seeking help for gambling problems: a review of the empirical literature," *Journal of Gambling Studies*, vol. 25, no. 3, pp. 407–424, 2009.

[21] L. Evans and P. H. Delfabbro, "Motivators for change and barriers to help-seeking in australian problem gamblers," *Journal of Gambling Studies*, vol. 21, no. 2, pp. 133–155, 2005.

[22] H. Suurvali, D. Hodgins, T. Toneatto, and J. Cunningham, "Treatment seeking among Ontario problem gamblers: results of a population survey," *Psychiatric Services*, vol. 59, no. 11, pp. 1343–1346, 2008.

[23] H. Tavares, M. L. Zilberman, F. J. Beites, and V. Gentil, "Gender differences in gambling progression," *Journal of Gambling Studies*, vol. 17, no. 2, pp. 151–159, 2001.

[24] B. Tolchard, L. Thomas, and M. Battersby, "GPs and problem gambling: can they help with identification and early intervention?" *Journal of Gambling Studies*, vol. 23, no. 4, pp. 499–506, 2007.

[25] G. Sanju and C. Gerada, "Problem gamblers in primary care: can GPs do more?" *The British Journal of General Practice*, vol. 61, no. 585, pp. 248–249, 2011.

[26] M. S. Rowan and C. S. Galasso, "Identifying office resource needs of Canadian physicians to help prevent, assess and treat patients with substance use and pathological gambling disorders," *Journal of Addictive Diseases*, vol. 19, no. 2, pp. 43–58, 2000.

[27] M. H. Christensen, C. A. Patsdaughter, and L. M. Babington, " Health care providers' experiences with problem gamblers," *Journal of Gambling Studies*, vol. 17, no. 1, pp. 71–79, 2001.

[28] M. Bazargan, M. Makar, S. Bazargan-Hejazi, C. Ani, and K. E. Wolf, "Preventive, lifestyle, and personal health behaviors among physicians," *Academic Psychiatry*, vol. 33, no. 4, pp. 289–295, 2009.

[29] E. E. Johnson, R. Hamer, R. M. Nora, B. Tan, N. Eisenstein, and C. Engelhart, "The lie/bet questionnaire for screening pathological gamblers," *Psychological Reports*, vol. 80, no. 1, pp. 83–88, 1997.

[30] J. McCambridge and J. Cunningham, "Against the odds: should GPS have any involvement with gambling problems?" *British Journal of General Practice*, vol. 57, article 327, no. 537, 2007.

[31] S. Sullivan, R. McCormick, M. Lamont, and A. Penfold, "Problem gambling: patients affected by their own or another's gambling may approve of help from general practitioners," *New Zealand Medical Journal*, vol. 120, no. 1257, p. U2605, 2007.

[32] A. Clarke, D. Lewis, I. Cole, and L. Ringrose, "A strategic approach to developing e-learning capability for healthcare," *Health Information and Libraries Journal*, vol. 22, supplement 2, pp. 33–41, 2005.

[33] A. Ritchie, "The Library's role and challenges in implementing an elearning strategy: a case study from northern Australia," *Health Information & Libraries Journal*, vol. 28, no. 1, pp. 41–49, 2011.

[34] J. Hackett, D. L. Madden, K. A. Viney, and C. Naylor, "Evaluation of three population health capacity building projects delivered by videoconferencing in NSW," *New South Wales Public Health Bulletin*, vol. 20, no. 11-12, pp. 182–186, 2009.

[35] O. Corazza, S. Assi, P. Simonato et al., "Promoting innovation and excellence to face the rapid diffusion of novel Psychoactive substances in the EU: the outcomes of the reDNet project," *Human Psychopharmacology*, vol. 28, no. 4, pp. 317–323, 2013.

[36] Confédération suisse O.f.d.l.s, Médecins et dentistes en 2012, 2013, http://www.bfs.admin.ch/bfs/portal/fr/index/themen/14/03/03/key/01.html.

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Research Article

Novel Psychoactive Substances in Young Adults with and without Psychiatric Comorbidities

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Objective. Comorbidities between psychiatric diseases and consumption of traditional substances of abuse (alcohol, cannabis, opioids, and cocaine) are common. Nevertheless, there is no data regarding the use of novel psychoactive substances (NPS) in the psychiatric population. The purpose of this multicentre survey is to investigate the consumption of a wide variety of psychoactive substances in a young psychiatric sample and in a paired sample of healthy subjects. *Methods*. A questionnaire has been administered, in different Italian cities, to 206 psychiatric patients aged 18 to 26 years and to a sample of 2615 healthy subjects matched for sex, gender, and living status. *Results*. Alcohol consumption was more frequent in the healthy young population compared to age-matched subjects suffering from mental illness (79.5% versus 70.7%; $P < 0.003$). Conversely, cocaine and NPS use was significantly more common in the psychiatric population (cocaine 8.7% versus 4.6%; $P = 0.002$) (NPS 9.8% versus 3%; $P < 0.001$). *Conclusions*. The use of novel psychoactive substances in a young psychiatric population appears to be a frequent phenomenon, probably still underestimated. Therefore, careful and constant monitoring and accurate evaluations of possible clinical effects related to their use are necessary.

1. Introduction

It is well known that mental disorders are accompanied by multiple comorbidities, but substance misuse is particularly common [1]. Many clinicians feel that substance misuse may be explained in some cases as a form of self-medication to improve psychopathology (depression, anhedonia, and negative symptoms) or to ameliorate the side effects of psychopharmacological treatment. Indeed, the cooccurrence between mental disorders and psychoactive substances misuse often leads to a more pernicious and difficult to treat course of illness, in terms of possible earlier age of onset, frequency and length of episodes, and diminished treatment compliance [2, 3]. Moreover, there is substantial evidence that substance misuse is a major risk factor for violence and aggression in patients with major mental disorders [4]. To

get an idea of the problem dimension as a health issue, in 2010 mental and substance use disorders accounted for 183.9 million disability-adjusted life years (DALYs) or 7.4% of all DALYs worldwide. Thus, considered together, mental and substance use disorders were the leading cause of years lived with disability (YLDs) worldwide [5]. The long-term consequences of increased reactivity (sensitisation) to episodes and substances misuse and their cross-sensitisation to each other may have a number of important implications for clinical therapeutics [2, 6]. The potential cross-sensitisation among stressors, episodes, and substances misuse raises the spectre of an adverse positive feedback mechanism in each domain of illness vulnerability, with recurrences of each not only increasing responsivity to itself, but also increasing responsivity to the others [2].

Recently, beyond "classic" substances of abuse, it seems that novel (new) psychoactive substances (NPS) are determining a further sanitary issue of growing importance, especially in relation to the fast-moving and potentially unlimited nature of their online market [7]. The term "novel psychoactive substances" (NPS) has been legally defined by European Union as a new narcotic or psychotropic drug, in pure form or in a preparation, that is not scheduled under the Single Convention on Narcotic Drugs of 1961 or the Convention on Psychotropic Substances of 1971, but may pose a public health threat comparable to that posed by substances listed in those conventions (Council of the European Union decision 2005/387/JHA) [8]. NPS are often almost unknown to health professionals, mainly due to the lack of evidence-based sources of information [9]. Since 1997, more than 200 novel psychoactive compounds have been reported; out of these, 41 were reported in 2010, 60 in 2011, and 57 in 2012 [7]. These substances are most often synthesized in underground laboratories, simply modifying the molecular structure of controlled drugs, hence raising further concerns in terms of the presence of contaminating agents [8]. The World Wide Web has emerged as a primary source of information about drugs in general and NPS in particular. Drug users can obtain information through online forums, chat rooms, and blogs and find out about new products. They can also communicate with other users about their experiences, the effects of the substances, and the recommended sources and routes of delivery. This may be an issue of concern if one considers that an estimated 61% of young European people aged between 15 and 24 years typically quote the Internet as a potential source of information on drugs [10]. The number of online shops offering to supply with NPS customers residing in European countries increased from 170 in January 2010 to 314 in January 2011 and 693 in January 2012 [7]. The possibility of purchasing NPS from web sites makes these drugs very easily available to vulnerable individuals, including children and adolescents. Vulnerable consumers are targeted by aggressive marketing strategies (attractive names, colourful packaging, and free samples to test); NPS appear to be mostly unregulated, and this may facilitate their popularity as well as the users' perception of risks associated with consumption. The idea that legality can equate with safety still remains well grounded amongst some recreational users [9].

Thus, the focus on novel psychoactive substances, peculiarly in youths, has become a diffuse topic of discussion in scientific literature, underlining a growing interest for this widespread phenomenon. However, still few epidemiological data about NPS diffusion exists. Recent data by European Monitoring Centre on Drugs and Drug Addiction (EMCDDA) highlights that small percentages of tested youths have experienced NPS (around 5%), most of them obtaining drugs from friends or at parties, rather than online [11]. A UK-based research found out that almost one-third of a sample of students (446) had tried NPS at least once in their life. A Polish epidemiological study on 14511 secondary school pupils and university students has registered NPS use rate of 4.49% and 1.83%, respectively [12]. The psychoactive substances abuse issue has been recently emphasized by researchers from all over the world: Madruga et al. have gathered information on a sample of 761 Brazilians aged from 14 to 19 years old; more than half of interviewed adolescents are regular alcohol users and one out of ten is an abuser and/or dependent, while nearly 3% has used an illicit substance in the twelve months before questionnaire administration [13]. Famuyiwa and colleagues supply epidemiologic data on 4286 school pupils (mean age 15.2 years) from Lagos, Nigeria, finding that 61.8% of respondents have used one or more psychoactive substances in their lifetime [14]. Currie reports results on *Salvia divinorum* consumption from Canada's Youth Smoking Survey (sample of 42179 Canadian adolescents aged 12–17 years), evidencing that 6.2% of the subjects has used the substance at least once in their life [15]. Kelly et al. have performed a field-based survey of 1740 patrons at nightlife venues in New York City. Within the sample, 8.2% reported use of synthetic cannabinoids and 1.1% reported use of mephedrone; the findings suggest that the use of synthetic cannabinoids and mephedrone among US nightlife scenes may remain relatively low in comparison with European nightlife scenes [16]. A recent study by Bruno et al. among 693 regular ecstasy users (REU) in Australia has evidenced that more than one quarter (28%) of REU have used a new psychoactive substance in the past six months, most commonly from the stimulant class (20%, typically mephedrone 17%) rather than from the psychedelic class (13%) [17]. These behaviours and patterns of use are encouraged by the increasing phenomenon of binge drinking, widely diffused in Europe and North America [18–20].

To the best of our knowledge, no current data exist about the use of NPS among psychiatric patients. This is the first study aiming to assess both the presence and the nature of NPS misuse in a population of Italian young adults in comparison with a psychiatry patient sample.

2. Materials and Methods

A questionnaire has been administered to a sample of 2615 healthy subjects, aged between 18 and 26 years. The instrument has been designed by comparing different theories and points of view about abuse and addiction. The data were collected between September 2013 and January 2014; the questionnaire was self-administered in an anonymous way by our

team of psychologists and psychiatrists, with the support of a peer-working group. We investigated socioeconomic characteristics (age, gender, residence, job status, level of education, and living status), alcohol use, and substance use (tobacco, caffeine, cannabis, and cocaine) with a peculiar focus on Novel Psychoactive Substances (NPS). The NPS we investigated are as follows: synthetic cannabinoids (spices), mephedrone (bath salts), methamphetamine (ice-shaboo-crystal meth), Ayahuasca, phenethylamines (Nbome-Fly-Solaris), *Salvia divinorum*, Kratom, gamma hydroxybutyric acid (GHB), methoxetamine (Special M), and desomorphine (krokodil).

The selected sample resided in different Italian cities, located in the north, centre, and south of the country, to ensure the inclusion of youths from diverse social and provenance contexts.

The same survey has been administered to a sample of 206 psychiatric patients, with DSM-5 fixed diagnoses at the time of test, excluding those with a substance use disorder. The patients were recruited in eight departments of mental health in various Italian cities, located in the north, centre, and south of the country to ensure a comparable sample. Healthy subjects were selected homogeneously by age, gender, and housing condition, following as a randomizing procedure the Snowball sampling [21]. The psychiatric subjects sample was composed of all the new inpatients admitted in the 8 recruiting centres in the period between December 2013 and March 2013.

Data collection was carried out in an anonymous and confidential way; all participants received a detailed explanation of the design of the study and a written informed consent was systematically obtained from every subject, according to the Declaration of Helsinki.

Baseline data were analysed using descriptive statistics, including means and standard deviations and frequencies and percentages. The chi-square (χ^2) test, Fisher's exact test, and nonparametric Wilcoxon-Mann-Whitney test were used for comparison of qualitative data. Quantitative variables were summarized by means and medians and compared using the Student's t-test. Factors with a P value lower than 0.25 were included in the multivariate analysis and P value lower than 0.05 was considered to be significant. SPSS version 14.0 was used for all analyses.

3. Results

The sample of 2615 healthy subjects consisted of 44.6% of males and of 55.4% of females, with a mean age of 22.01 ± 2.6 years. The sociodemographic data indicated that the majority of respondents had attended high school (66.6%), was living with parents (67.4%), and was a student (59%).

On the other hand, the sample of 206 psychiatric patients (20.9% diagnosed with schizophrenia or other psychotic disorders, 15.5% with depressive disorders, 13.1% with bipolar disorder, 27.2% with anxiety disorders, 17% with personality disorders, and 6.3% with Obsessive Compulsive Disorder) was composed of 45.6% males and 54.4% of females, with a mean age of 22.4 ± 2.7 years. 63.8% of patients had attended high school, 75.5% was living with parents, and 37.4% was a student at the time of testing (Table 1).

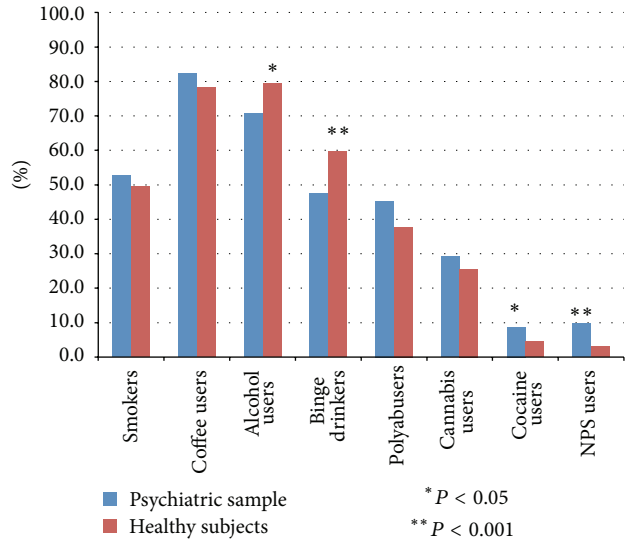

Figure 1: Psychoactive substances.

Habitual consumption of alcoholic beverages was significantly more common in healthy subjects than in patients (79.5% versus 70.7%; $P < 0.003$), as well as Binge Drinking behaviours (59.7% versus 47.6%; $P < 0.001$).

With regard to the association of alcohol consumption with use of other substances (37.8% in healthy subjects and 45.3% in patients), there was no statistically significant difference between two groups.

The data on the consumption of drugs indicated that the difference in cannabis use between the two groups (25.6% in healthy subjects and 29.3% in patients) was not statistically significant, while both cocaine (8.7% versus 4.6%; $P = 0.002$) and NPS use (9.8% versus 3%; $P < 0.001$) prevailed among patients.

The differences in coffee consumption (80.4% in healthy subjects and 82.4% in patients) and cigarettes smoking (46.7% in healthy subjects and 52.7% in patients) were not statistically significant between the two groups (Figure 1).

Regarding the consumption of substances in the sample of psychiatric patients, those with a diagnosis of schizophrenia and other psychotic disorders used to consume alcohol in 65.6% of cases, had binge drinking behaviours in 51.2% of cases, used cannabinoids in 41.9% of cases, consumed cocaine in 9.3% of cases, and used NPS in 9.3% of cases; those diagnosed with depressive disorders consumed alcohol in 75% of cases, with a binge prevalence of 53.1%; cannabinoids were used in 21.9% of cases, cocaine in 6.3%, and NPS in 15.6%. Patient with a diagnosis of bipolar disorder consumed alcohol in 88.9% of cases, with concomitant binge drinking in 70.4% of the sample; use of cannabinoids was evidenced in 48.1% of cases, cocaine in 18.5%, and NPS in 14.8%. Those diagnosed with anxiety disorders consumed alcohol in 66.1% of cases, with a prevalence of binge behaviours of 41.1%; use of cannabinoids was reported in 14.3% of cases, cocaine in 5.4%, and NPS in 8.9%. Patients diagnosed with personality

Table 1: Sociodemographic characteristics.

Variable	Psychiatric patients (%)	Healthy subjects (%)
Age	21.4 ± 2.7 years	22.01 ± 2.6 years
Gender	Male: 45.6%	Male: 44.6%
	Female: 56.4%	Female: 55.4%
Level of educational	Primary degree: 1.5%	Primary degree: 0.2%
	Middle school: 21.7%	Middle school: 8%
	High school: 63.1%	High school: 66.6%
	University: 13.8%	University: 25.1%
Job status	Student: 37.4%	Student: 59%
	Student/worker: 8.7%	Student/worker: 10.8%
	Worker: 22.3%	Worker: 19.7%
	Unemployed: 31.6%	Unemployed: 10.5%
Living status	Parents: 75.5%	Parents: 67.4%
	Friends: 9.3%	Friends: 20.6%
	Alone: 10.3%	Alone: 8.1%
	Partner: 4.9%	Partner: 4%
Psychiatric diagnosis (DSM-5)	Psychotic Disorders: 20.9%	—
	Depressive disorders: 15.5%	—
	Bipolar disorder: 13.1%,	—
	Anxiety disorders: 27.2%	—
	Personality disorders: 17%	—
	DOC: 6.3%	—

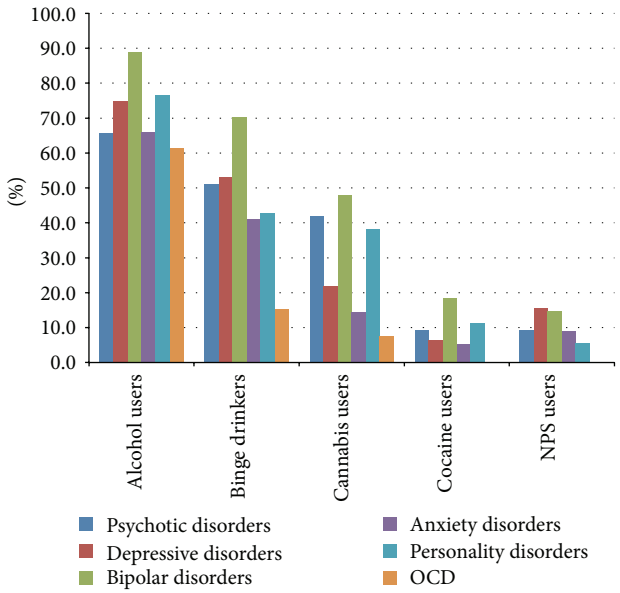

Figure 2: Psychoactive substances use in psychiatric patients.

disorder drank alcohol in 76.5% of cases, had binge drinking behaviours in 42.9% of cases, and used cannabinoids in 38.2% of cases, cocaine in 11.4%, and NPS in 5.7%. Those diagnosed with DOC consumed alcohol in 61.5% of cases, with a binge prevalence of 15.4%; they smoked cannabinoids in 7.7% of cases but did not use cocaine or NPS (Figure 2).

More specifically, with regard to the use of NPS, our data revealed that among healthy subjects 1.6% had experimented with methamphetamine, 1.1% with *Salvia divinorum*, 1% with synthetic cannabinoids, 0.6% with phenethylamines, 0.3% with mephedrone, 0.3% with GHB, 0.2% with Ayahuasca, 0.2% with methoxetamine, 0.2% with desomorphine, and 0.1% with kratom.

In the psychiatric patients' sample, we evidenced that 5.8% used Synthetic Cannabinoids, 3.4% methamphetamine, 1.9% GHB, 1% *Salvia divinorum*, 1% methoxetamine, 0.5% mephedrone, 0.5% Ayahuasca, 0.5% phenethylamines, 0% kratom, and 0% desomorphine (Table 2).

4. Conclusions

To the best of our knowledge, this is the first paper providing some data about NPS misuse in psychiatric patients; nevertheless, it is well known that psychiatric patients are much more likely to have a substance or alcohol abuse problem than general population [22–24].

Our results show a higher prevalence of habitual consumption of alcohol and binge drinking behaviours in healthy subjects in comparison with psychiatric patients. These data may be explained with the widespread social use of alcohol and with the concept of the "drink in the company" as a social glue, while it is known that psychiatric conditions lead to marginalization and isolation. Another reason may be related to the continuous contact of psychiatric patients with medical figures and drug therapies, which might contribute to a reduction in the consumption of alcohol [25, 26].

Table 2: Percentage use NPS.

Types of novel psychoactive substances	Percentage use (%)	
	Healthy subjects	Patients
"Spices" *Synthetic cannabinoids*	1%	5.8%
"Bath salts" *Mephedrone*	0.3%	0.5%
"Ice-shaboo-crystal meth" *Methamphetamine*	1.6%	3.4%
Ayahuasca	0.2%	0.5%
"Nbome-fly-solaris" *Phenethylamines*	0.6%	0.5%
Salvia divinorum	1.1%	1%
Kratom	0.1%	0%
"Ghb" *Gamma hydroxybutyric acid*	0.3%	1.9%
"Special m" *Methoxetamine*	0.2%	1%
"Krokodil" *Desomorphine*	0.2%	0%

On the other side, the consumption of NPS and cocaine was significantly higher in the patients group than among healthy subjects. These data may have different meanings: firstly, there is the possibility that the use of these substances is itself a factor able to trigger prodromal symptoms to full development; on the other hand, subjects with psychiatric disorder may be more motivated to try compounds considered harmful and/or illegal, possibly as self-medication agents. These are of course only speculations not fully justified by our data, but may represent future hypothesis that need to be investigated. The presence of a quite high percentage of patients with a diagnosis in the area of psychotic and bipolar disorders associated with the use of cannabis is of clinical interest. From our data it is not possible to understand if cannabis use represents a predisposing factor. However, this association gives further emphasis to the debated issue of a relationship between cannabis and major psychiatric disorders [3, 27, 28]. Other data on substances consumption registered for different psychiatric diagnoses were suggestive and worthy of interest despite being limited by the smallness of the subgroups.

In our study, the use of NPS in healthy subjects and psychiatric patients is statistically in favour of the patients group (9.8% versus 3%; $P < 0.001$). The situation of NPS consumption in Europe, in response to recent developments in EU drug market, is analysed by the Eurobarometer "Youth attitudes on Drugs". The survey asked adolescents and young adults about their experiences and attitudes towards new psychoactive substances. The sample included over 12000 youths aged 15–24, randomly selected across the 27 EU Member States. Overall, 5% of the participants reported having used NPS: Ireland (16%), Poland (9%), Latvia (8.8%) and United Kingdom (8%) were way above the mean, while Italy (0.8%), Finland (1%) and Greece (1.6%) were at the bottom of the list [29]. On the other hand, our recent Italian data showed a higher percentage of NPS consumption in healthy subjects, as well as a considerable higher percentage in psychiatric patients. This could be due to selection biases, but it is also possible that the extent of NPS consumption may be growing or it was previously underestimated.

In our sample, we have evidenced a relevant of use of synthetic cannabinoids among both patients (5.8%) and healthy controls (1%). Being one of the most known and used NPS, synthetic cannabinoids may represent a significant health issue. Moreover, Spice use is apparently gaining popularity among teenagers and young adults in the US, and a European survey found similar figures, with a 7% prevalence of lifetime use in a sample aged 15 to 18 years [30, 31]. The strong psychotogenic action of synthetic cannabinoids is supposed to be due to their higher affinity for cannabinoid receptors and to their lower concentration of cannabidiol [32, 33]. Papanti et al. recently coined the term "Spiceophrenia," to define the peculiar psychopathological characteristics of spice-induced psychosis: according to their assumptions, it is possible to hypothesize that the use of synthetic cannabinoids may "trigger" the occurrence or the relapse of psychosis in psychosis-vulnerable individuals or in patients with a prodromal psychotic syndrome [34].

Cathinones derivatives, and especially mephedrone, have become a particularly widespread phenomenon in the UK in 2010, with a peak of 23.4% of Scottish students who had used the substance at least once in their life [35, 36]. In our sample, mephedrone was used by 0.3% of healthy subjects and 0.5% of psychiatric patients. Mephedrone core activity is mainly stimulant-like, with desired effects such as mood enhancement and alertness, but may also determine the development of hallucinogenic symptoms, anxiety, agitation, and confusion, with unpredictable consequences, especially in nonhealthy users [37].

Our results indicated other potentially alarming trends of misuse, such as phenethylamines and derivatives (0.6% in healthy controls and 0.5% in patients), *Salvia divinorum* (1.1% in healthy subjects and 1% in psychiatric sample), and even pharmaceutical products (e.g., 0.3% of healthy sample and 1.9% of patients declared to have assumed GHB for recreational purpose).

Clinicians could argue that NPS may reduce the efficacy of the treatments for psychiatric disorders, worsen symptoms, and reduce the adherence to therapeutic plans. On the other hand, health and other professionals should be rapidly and accurately informed about these new and serious trends of misuse. A questionnaire administered to professionals from the departments of addiction, psychiatry, and paediatrics and emergency room in Italy has highlighted that interviewees self-reported a poor technical knowledge of NPS. 27% of the respondents confirmed not being aware if their patients had a previous history of NPS misuse and most health professionals appeared to have concerns relating to associated medical and psychopathological risks, especially in terms of aggression/psychomotor agitation. Overall, most respondents reported the need to have better access to NPS-related reliable sources of information [38].

The use of NPS represents therefore a serious issue from both a clinical and a public health point of view. For these reasons, careful and constant monitoring, accurate evaluation of possible clinical effects related to their use, and development of prevention measures are necessary to tackle the wide escalation of NPS and to contribute in improving the quality of public health on a global level.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] K. R. Merikangas, R. Herrell, J. Swendsen, W. Rossler, V. Ajdacic-Gross, and J. Angst, "Specificity of bipolar spectrum conditions in the comorbidity of mood and substance use disorders: results from the Zurich cohort study," *Archives of General Psychiatry*, vol. 65, pp. 47–52, 2008.

[2] RM. Post and P. Kalivas, "Bipolar disorder and substance misuse: pathological and therapeutic implications of their comorbidity and cross-sensitisation," *The British Journal of Psychiatry*, vol. 202, no. 3, pp. 172–176, 2013.

[3] G. Martinotti, G. Di lorio, D. Tedeschi et al., "Prevalence and intensity of basic symptoms among cannabis users: an observational study," *The American Journal of Drug and Alcohol Abuse*, vol. 37, no. 2, pp. 111–116, 2011.

[4] M. Soyka, " Substance misuse, psychiatric disorder and violent and disturbed behaviour," *The British Journal of Psychiatry*, vol. 176, pp. 345–350, 2000.

[5] H. A. Whiteford, L. Degenhardt, J. Rehm et al., "Global burden of disease attributable to mental and substance use disorders: findings from the global burden of disease study 2010," *The Lancet*, vol. 382, no. 9904, pp. 1575–1586, 2013.

[6] G. Martinotti, V. Carli, D. Tedeschi et al., "Mono- and polysubstance dependent subjects differ on social factors, childhood trauma, personality, suicidal behaviour, and comorbid axis I diagnoses," *Addictive Behaviors*, vol. 34, no. 9, pp. 790–793, 2009.

[7] European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), *European Drug Report 2013: Trends and Developments*, European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Lisbon, Portugal, 2013.

[8] United Nations Office on Drugs and Crime (UNODC), World Drug Report, United Nations Publication, Sales No. E.13.XI.6.

[9] O. Corazza, S. Assi, P. Simonato et al., "Promoting innovation and excellence to face the rapid diffusion of Novel Psychoactive Substances in the EU: the outcomes of the ReDNet project," *Human Psychopharmacology*, vol. 28, pp. 317–323, 2013.

[10] Eurobarometer, Young people and drugs: analytical report, 2009, http://ec.europa.eu/public_opinion/flash/fl_233_en.pdf.

[11] European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), *Annual Report on the State of the Drugs Problem in Europe*, Lisbon, Portugal, November 2012, http://www.emcdda.europa.eu/publications/annual-report/2012.

[12] P. Biliński, L. Kapka-Skrzypczak, and P. Jabłoński, "Determining the scale of designer drugs (DD) abuse and risk to public health in Poland through an epidemiological study in adolescents," *Annals of Agricultural and Environmental Medicine*, vol. 19, no. 3, pp. 357–64, 2012.

[13] C. S. Madruga, R. Laranjeira, R. Caetano et al., "Use of licit and illicit substances among adolescents in Brazil—a national survey," *Addictive Behaviors*, vol. 37, pp. 1171–1175, 2012.

[14] O. Famuyiwa, O. F. Aina, and O. M. Bankole-Oki, "Epidemiology of psychoactive drug use amongst adolescents in metropolitan Lagos, Nigeria," *European Child and Adolescent Psychiatry*, vol. 20, no. 7, pp. 351–359, 2011.

[15] C. L. Currie, "Epidemiology of adolescent Salvia divinorum use in Canada," *Drug and Alcohol Dependence*, vol. 128, no. 1-2, pp. 166–170, 2013.

[16] B. C. Kelly, B. E. Wells, M. Pawson, A. Leclair, J. T. Parsons, and S. A. Golub, "Novel psychoactive drug use among younger adults involved in US nightlife scenes," *Drug and Alcohol Review*, vol. 32, no. 6, pp. 588–593, 2013.

[17] R. Bruno, A. J. Matthews, M. Dunn et al., "Emerging psychoactive substance use among regular ecstasy users in Australia," *Drug and Alcohol Dependence*, vol. 124, no. 1-2, pp. 19–25, 2012.

[18] Special Eurobarometer 331 (European Commission). Eu citizens' attitudes towards alcohol, Brussels, Belgium, 2010.

[19] N. M. Bekman, J. L. Winward, L. L. Lau, C. C. Wagner, and S. A. Brown, "The impact of adolescent binge drinking and sustained abstinence on affective state," *Alcoholism: Clinical and Experimental Research*, vol. 37, no. 8, pp. 1432–1439, 2013.

[20] M. Lupi, T. Acciavatti, R. Santacroce, E. Cinosi, G. Martinotti, and M. di Giannantonio, ""Drunkorexia": a pilot study in an italian sample," *Research and Advances In Psychiatry*, vol. 1, no. 1, pp. 1–5, 2014.

[21] L. A. Goodman, "Snowball sampling," *Annals of Mathematical Statistics*, vol. 32, pp. 148–170, 1961.

[22] J. J. Blanchard, S. A. Brown, W. P. Horan, and A. R. Sherwood, "Substance use disorders in schizophrenia: reviews, integration and a proposed model," *Clinical Psychological Review*, vol. 20, pp. 207–234, 2000.

[23] D. F. Zullino, L. Waber, and Y. Khazaal, "Cannabis and the course of schizophrenia," *The American Journal of Psychiatry*, vol. 165, no. 10, pp. 1357–1358, 2008.

[24] K. R. Muller-Vahl and H. M. Emrich, "Cannabis and schizophrenia: towards a cannabinoid hypothesis of schizophrenia," *Expert Review of Neurotherapeutics*, vol. 8, no. 7, pp. 1037–1048, 2008.

[25] G. Martinotti, M. Di Nicola, D. Tedeschi et al., "Pregabalin versus naltrexone in alcohol dependence: a randomised, double-blind, comparison trial," *Journal of Psychopharmacology*, vol. 24, no. 9, pp. 1367–1374, 2010.

[26] G. Martinotti, M. Lupi, F. Sarchione et al., "The potential of pregabalin in neurology, psychiatry and addiction: a qualitative overview," *Current Pharmaceutical Design*, vol. 19, no. 35, pp. 6367–6374, 2013.

[27] G. Martinotti, G. Di Iorio, G. Sepede, D. De Berardis, L. De Risio, and M. Di Giannantonio, "Cannabis use and psychosis: theme introduction," *Current Pharmaceutical Design*, vol. 18, no. 32, pp. 4991–4998, 2012.

[28] G. di Iorio, M. Lupi, S. Fabiola et al., "The endocannabinoid system: a putative role in neurodegenerative diseases," *International Journal of High Risk Behaviors and Addiction*, vol. 2, no. 3, pp. 100–106, 2013.

[29] European Commission, "Youth attitudes on drugs," Flash Eurobarometer 330, 2011, http://ec.europa.eu/public_opinion/flash/fl_330_en.pdf.

[30] M. B. Forrester, "Adolescent synthetic cannabinoid exposures reported to Texas Poison Centers," *Pediatric Emergency Care*, vol. 28, no. 10, pp. 985–999, 2012.

[31] C. Mongerstern and B. Werse, Proceedings of the 1st International Conference on Toxicity, Risk Profiles, Legal Control and Prevalence of Synthetic Cannabinoids, Conference Handout—Conference on SPICE Prevention Issues, 2012, http://www.uniklinik-freiburg.de/rechtsmedizin/live/SpiceConference/ConferenceHandout.pdf.

[32] L. Fattore and W. Fratta, "Beyond THC: the new generation of cannabinoid designer drugs," *Frontiers in Behavioral Neuroscience*, vol. 5, pp. 1–12, 2011.

[33] A. W. Zuardi, J. A. Crippa, J. E. Hallak, F. A. Moreira, and F. S. Guimarães, "Cannabidiol , a Cannabis sativa constituent, as an antipsychotic drug," *Brazilian Journal of Medical and Biological Research*, vol. 39, no. 4, pp. 421–429, 2006.

[34] D. Papanti, F. Schifano, G. Botteon et al., ""Spiceophrenia": a systematic overview of "Spice"-related psychopathological issues and a case report," *Human Psychopharmacology*, vol. 28, no. 4, pp. 379–389, 2013.

[35] S. D. Brandt, H. R. Sumnall, F. Measham, and J. Cole, "Analyses of second-generation "legal highs" in the UK: initial findings," *Drug Testing and Analysis*, vol. 2, no. 8, pp. 377–382, 2010.

[36] P. I. Dargan, S. Albert, and D. M. Wood, "Mephedrone use and associated adverse effects in school and college/university students before the UK legislation change," *QJM*, vol. 103, pp. 875–879, 2010.

[37] F. Schifano, A. Albanese, S. Fergus et al., "Mephedrone (4-methylmethcathinone; "meow meow"): chemical, pharmacological and clinical issues," *Psychopharmacology*, vol. 214, no. 3, pp. 593–602, 2011.

[38] P. Simonato, O. Corazza, P. Santonastaso et al., "Novel psychoactive substances as a novel challenge for health professionals: results from an Italian survey," *Human Psychopharmacology*, vol. 28, no. 4, pp. 324–331, 2013.

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Research Article

Video Game Addiction in Gambling Disorder: Clinical, Psychopathological, and Personality Correlates

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Objective. We studied the prevalences of video game use (VGU) and addiction (VGA) in gambling disorder (GD) patients and compared them with subjects with non-video game use (non-VGU) in relation to their gambling behavior, psychopathology, and personality characteristics. *Method*. A sample of 193 GD patients (121 non-VGU, 43 VGU, and 29 VGA) consecutively admitted to our pathological gambling unit participated in the study. *Assessment*. Measures included the video game dependency test (VDT), symptom checklist-90-revised, and the temperament and character inventory-revised, as well as a number of other GD indices. *Results*. In GD, the observed prevalence of VG (use or addiction) was 37.3% (95% CI:30.7% ÷ 44.3),VGU 22.3% (95% CI:17.0% ÷ 28.7), and VGA 15% (95% CI:10.7% ÷ 20.7). Orthogonal polynomial contrast into logistic regression showed positive linear trends for VG level and GD severity and other measures of general psychopathology. After structural equation modeling, higher VG total scores were associated with younger age, general psychopathology, and specific personality traits, but not with GD severity. Patients' sex and age were involved in the mediational pathways between personality traits and VG impairment. *Conclusions*. GD patients with VG are younger and present more dysfunctional personality traits, and more general psychopathology. The presence of VG did not affect the severity of GD.

1. Introduction

Research on gambling disorder (GD) is relatively new. In fact it was not until 1980 that the diagnostic and statistical manual of mental disorders, in its third edition (DSM-III), formally recognized this disorder (then was called pathological gambling) and included it in impulse- control disorders not elsewhere classified. Recently, in the DSM-5 [1], the nosological nature of the disorder was changed after reviewing the existing literature and evidence [2]; it was renamed as

gambling disorder (GD) and classified in a new section called *Substance Related and Addictive Disorders*. Moreover, the illegal acts criterion was removed, the cut-off for the diagnosis of GD was modified from five to four criteria, and it was specified that symptoms had to be present for a period of 12 months [3].

During the review of the manual all possible nonsubstance addictions were analyzed, that is, pathological gambling, internet gaming, more general use of the Internet, shopping, exercise, and work. Finally, only GD was classed as a nonsubstance addiction, due to its clinical similarities, phenomenology, comorbidity, and treatment response with substance use disorders (SUDs) and also due to its shared neurobiological factors [4, 5].

However, the working committee of the DSM-5 decided to place Internet gaming disorder (IGD) in Section 3, which includes potential problems that require further investigation. This decision was based on the growing number of clinical and population studies of the disorder and its severe individual and interpersonal consequences [6]. Additionally, certain similarities in neurobiological features [7, 8], psychiatric comorbidity, and personality traits (sensation seeking, impulsivity, and low self-esteem) have recently been found between IGD with SUDs and GD [9]. Given that a wide range of tools and criteria have been used in the IGD scientific literature, it was decided to establish a set of nine diagnostic criteria, of which five or more must be present for a period of 12 months in order to standardize the definition and diagnosis of IGD [2, 6]. The inclusion of this condition in the DSM-5 will undoubtedly have a significant impact not only on future research [10] but also on the more clinical aspects such as destigmatization and improvements in diagnosis and treatment [11].

Although game users in industrialized countries tend to be over 18 [12], few studies have explored IGD in adult populations. Most of the ones carried out to date have been conducted in Europe [13–16]. All coincide in indicating the association between the use of massively multiplayer online role-playing games (MMORPGs) and problematic or addictive behavior. Prevalence rates range between 0.2% and 1.3% for addictive use and 3.3% and 4.1% for problematic behavior [14–16]. However, the study by Achab et al. [13] in an adult population, which adapted the DSM-IV-TR diagnostic criteria [17] for substance dependence disorders to MMORPGs, reported an addiction rate as high as 27.5%. The disparity of the results may be due to the differences in the assessment tools used by the studies or in the target population investigated (as suggested by King et al. [18]); while some studies concentrated on specific adult users more prone to developing addictive behaviors [13], others concentrated on young populations [19, 20]. However, several authors noted specific factors common to all participants (e.g., withdrawal, loss of control, high rates of tolerance, social and financial problems, problems with relatives, as well as mood swings, anxiety, irritability, sedentary lifestyle, decreased sleep, and abandonment of obligations, responsibilities, and leisure activities) [6, 11, 16, 18].

Other sociodemographic and clinical variables associated with adult IGD were age (the condition being more common in younger adults), higher education, residence in urban areas, and early age of onset [13]. The same features have been described in GD [21, 22]. In addition, both disorders have been associated with psychopathology such as depression, anxiety, and impulse-control disorders [6, 11, 23] and with dysfunctional personality traits such as high impulsivity and sensation seeking, neuroticism, introversion, and hostility [11, 24, 25].

The few studies that have compared GD with general new technology addiction [26–29] coincide in reporting high levels of psychopathology and maladaptive personality traits in both disorders. However, most of them do not differentiate between IGD and the problem of more general use of the network or Internet addiction (IA). Tonioni et al. [28] reported not only similarities in relation to the association of depression, anxiety, and overall functioning but also differences in social patterns. Social skills were lower in the IA group, who presented lower social acceptance, cooperation, and social support in general. Regarding personality traits, both groups had low scores on reward dependence and self-directedness and high scores on self-transcendence. However, Muller et al. [29] identified higher neuroticism, lower conscientiousness, and extraversion in patients with IGD, the last two being statistical predictors of the condition. For Kuss [11], despite the existence of vulnerability factors common to the two disorders such as the involvement of brain reward circuits, impulsivity, deficits in executive functions, and attention, there were also marked clinical differences, apart from the preoccupation and obsessive use observed in both.

Although some studies have explored differences and commonalities between GD and IGD/VG, few have analyzed the use and abuse of VG in GD. Based on the results of previous studies [28], we hypothesized that there would be more similarities than differences between three groups of GD patients divided according to level of video game use: non-video game users (non-VGU), video game users (VGU), and video game addicts (VGA). However, we expected the group with GD plus VGA to display more severe psychopathology and dysfunctional personality traits (viz., higher levels of persistence, defined as perseverance in behavior despite frustration or fatigue).

Given the current lack of studies in clinical samples, especially in adult populations, the present study had three main goals: (1) to assess the current presence of video game addiction (VGA) symptoms in GD, (2) to establish whether the presence of VGA symptoms is associated with greater severity of GD symptomatology and general psychopathology, and (3) to assess whether the presence of more VGA symptoms is associated with specific temperament and character personality traits in GD patients.

2. Method

2.1. Participants. A total of 193 treatment-seeking GD patients participated in the current study (167 males and 26 females), consecutive referrals for assessment, and outpatient treatment at the Pathological Gambling Unit of the Psychiatric Department at the University Hospital of Bellvitge, Barcelona, Spain, 2013. All patients were diagnosed

Table 1: Sociodemographic and clinical characteristics of the GD sample ($N = 193$) and comparisons between groups.

	Total $n = 193$	[1]Non-VGU $n = 121$	[1]VGU $n = 43$	[1]VGA $n = 29$	P
Gender; *n* (%)					
Males	167 (86.5%)	103 (85.1%)	39 (90.7%)	25 (86.2%)	0.654
Females	26 (13.5%)	18 (14.9%)	4 (9.3%)	4 (13.8%)	
Age (years); mean (SD)	42.4 (13.4)	45.2 (13.6)	37.3 (12.0)	38.6 (11.1)	0.001
Employed; *n* (%)	99 (51.3%)	61 (50.4%)	23 (53.5%)	15 (51.7%)	0.941
Marital status: single; *n* (%)	64 (33.2%)	37 (30.6%)	16 (37.2%)	11 (37.9%)	0.613
Smoker; *n* (%)	109 (56.5%)	66 (54.5%)	23 (53.5%)	20 (69.0%)	0.336
Use of alcohol; *n* (%)	35 (18.1%)	20 (16.5%)	7 (16.3%)	8 (27.6%)	0.358
Use of substances; *n* (%)	14 (7.3%)	10 (8.3%)	3 (7.0%)	1 (3.4%)	0.666
Age of onset PG problems; mean (SD)	15.7 (10.8)	17.2 (11.5)	11.7 (9.0)	15.4 (9.2)	0.024
Duration of PG; mean (SD)	5.94 (7.0)	5.87 (6.8)	5.03 (7.5)	7.58 (7.0)	0.370
Main gambling; *n* (%)					
Slot machines	123 (63.7%)	77 (63.6%)	26 (60.5%)	20 (69.0%)	0.762
Bingo	12 (6.2%)	11 (9.1%)	1 (2.3%)	0 (0%)	
Lotteries	13 (6.7%)	11 (9.1%)	1 (2.3%)	1 (3.4%)	
Casino	8 (4.1%)	5 (4.1%)	3 (7.0%)	0 (0%)	
Other	37 (19.2%)	17 (14.0%)	12 (27.9%)	8 (27.6%)	

SD: standard deviation. [1]Non-VGU (non-video game users) (total VDT score of 0); VGU: video game users (total VDT score between 1 and 19); VGA: video game addicts (total VDT score of 20 or higher). Chi-square test for categorical outcomes and ANOVA for quantitative outcomes.

according to DSM-IV criteria using Stinchfield's diagnostic questionnaire for pathological gambling [30, 31], conducted by experienced psychologists and psychiatrists. The majority of GD patients were slot machine gamblers (63.7%; $N = 123$). According to the video game dependency test (VDT), GD patients were assigned post hoc to three groups: 121 (62.7%) with total VDT scores of 0 to the non-video game user group (non-VGU), 43 (22.3%) with total VDT scores between 1 and 19 to the video game user group (VGU), and 29 (15%) with total VDT scores 20 or more to the video game addict group (VGA). All were Internet gaming players.

As shown in Table 1, the mean age of the sample was 42.4 years old (SD = 13.4). Most subjects were employed (51.3%) and 33.2% were single or without a partner. Problem alcohol use was recorded in 18.1%, and substance abuse in 7.3%.

2.2. Instruments. A comprehensive assessment battery was administered which measured GD and VGA symptoms, sociodemographic characteristics, general psychopathology, and personality traits. The battery included internationally applied instruments in the GD field, such as the South Oaks Gambling Screen (SOGS) [32, 33] and Stinchfield's diagnostic questionnaire for pathological gambling according to DSM-IV criteria [30, 31]. A validated Spanish-language scale entitled video game dependency test (*Test de Dependencia de Videojuegos*—VDT) [34], the symptom checklist-revised (SCL-90-R) [35], and the temperament and character inventory-revised [36] were also used.

2.2.1. South Oaks Gambling Screen (SOGS) [33]. The SOGS includes 20 items that produce a total score ranging from 0 to 20, with higher values indicating more severe psychopathology, and a score of five or more indicating probable pathological gambling (PG—now renamed as "gambling disorder" in DSM-5 [3, 37]). The psychometric properties of the Spanish version of the questionnaire have been shown to be satisfactory. Test-retest reliability was $r = 0.98$ and internal consistency was 0.94 (Cronbach's α). Convergent validity with regard to DSM-III-R criteria for pathological gambling [38] has been estimated at $r = 0.92$ [39]. Furthermore, several studies in both clinical and general population samples have reported that the SOGS presents satisfactory psychometric properties as an index of gambling problem severity [40–42].

2.2.2. Stinchfield's Diagnostic Questionnaire for Pathological Gambling according to DSM-IV Criteria [30, 31]. This questionnaire measures the ten DSM-IV diagnostic criteria for PG with 19 items [43]. This scale has demonstrated satisfactory psychometric properties. Internal consistency, measured with Cronbach's alpha, yielded values of $\alpha = 0.81$ for the general population and $\alpha = 0.77$ for a gambling treatment group. Convergent validity was estimated with a correlation with the SOGS as $r = 0.77$ for a general population sample and $r = 0.75$ for a gambling treatment sample. This scale has been adapted for the Spanish population by Jimenez-Murcia, Stinchfield, and colleagues [31] and has demonstrated adequate psychometric properties. Cronbach's alpha in the present sample was very good ($\alpha = 0.90$).

Video game dependency test (Test de Dependencia de Videojuegos—VDT) [34] is a reliable and valid 25-item self-report scale that assesses video game dependence and video game addiction. The test incorporates four factors that make up the principal characteristics of dependence: withdrawal,

tolerance, problems caused by excessive use, and lack of control. Of these factors, as expected, withdrawal (defined as the distress arising from not being able to play video games and using games as a means of coping with adverse emotional states) accounts for the greatest part of the variance. The VDT total score is an indicator of video game addiction, with a cut-off score of 20. Internal consistency for the VG total score in the sample was excellent (alpha = 0.97). ROC procedures selected 20 as the best cut-off for the raw score, with a sensitivity of 80.0% and a specificity of 86.7% (area under the ROC curve = 0.80, $P = 0.024$).

2.2.3. Temperament and Character Inventory-Revised (TCI-R) [36]. This is a 240-item questionnaire with 5-point Likert response options [44]. It measures seven dimensions of personality: four temperaments (harm avoidance, novelty seeking, reward dependence, and persistence) and three characters (self-directedness, cooperativeness, and self-transcendence). The Spanish version of the inventory has demonstrated satisfactory psychometric properties, ranging between 0.77 and 0.84 [45, 46].

2.2.4. Symptom Check List 90-Item-Revised (SCL-90-R) [35]. The SCL-90-R measures a broad range of psychological problems and psychopathology symptoms. The questionnaire contains 90 items and measures nine primary symptom dimensions: somatization, obsessive/compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. It also includes three global indices: a global severity index (GSI), designed to measure overall psychological distress; a positive symptom distress index (PSDI), designed to assess symptom intensity; and a positive symptom total (PST), which reflects self-reported symptoms. The GSI can be used as a summary of the subscales. Evaluation of the revised Spanish-language version generated an internal consistency (coefficient alpha) of 0.75 [35, 47].

Additional demographic, clinical, and social/family variables related to gambling were evaluated using a semistructured face-to-face clinical interview described elsewhere [48].

2.3. Procedure. In accordance with our unit's assessment protocol and treatment model published elsewhere [48], we carried out a specific semistructured interview and functional analysis of GD. All the information was collected during the first interview. The remaining psychometric assessments mentioned above were administered to all subjects in a second session. Both interviews were conducted in a time frame of one week by a psychologist and a psychiatrist (each with more than 15 years of work experience in this field). GD patients were assigned to the three VG groups (non-VGU, VGU, and VGA) as described in Section 2.1 above. The Ethics Committee of the University Hospital of Bellvitge (Barcelona, Spain) approved the study, and informed consent was obtained from all participants.

2.4. Statistical Analysis. Analyses were carried out with SPSS20 for Windows. The three VG groups were compared through logistic regression for dichotomous outcomes and with ANOVA procedures for quantitative data. For both models (logistic regression and ANOVA), the VG groups were entered as independent variables and the variables measuring the GD related measures were considered the criteria. Orthogonal polynomial contrasts (used for grouping-ordered independent factors) performed a trend analysis to test patterns in data, the presence of linear and/or quadratic trends ($k - 1 = 2$ order comparisons were assessed, linear and quadratic trends, due to the $k = 3$ levels of the grouping variable). Cohen's d was used to measure the effect size for pairwise comparison between groups (effect size was considered low with $|d| < 0.50$, moderate with $|d| > 0.50$, and high with $|d| > 0.80$).

Partial correlations, adjusted for the participants' sex and age, evaluated the association between VG total score (considered as a dimensional-metric variable) and clinical measures.

Stepwise multiple regression and binary logistic regression selected the best predictors of the VG scores (for each scale and for the binary classification based on the cut-off = 20), considering as input variables the participants' sex, age, employment status, marital status, and personality profile (TCI-R scores).

The mediational hypotheses were tested through structural equation models (SEM) with STATA13 for Windows. Overall goodness-of-fit statistics were assessed through χ^2 test, the root mean squared error of approximation (RMSEA), baseline comparison index (comparative fit index CFI), and residual size (standardized mean squared residual SMSR). A fit was considered to be good if [49] a nonsignificant result ($P > 0.05$) was achieved in the χ^2 test, if the RMSEA was lower than .08, if the CFI coefficients were higher than 0.90, and if SRMR was limited to 0.08. The equation level goodness-of-fit and the effect sizes were also estimated through R^2 coefficients for each equation and for the global model (these coefficients evaluated the fraction of variance explained by the indicator/indicators), multiple correlation (mc), and Bentler-Raykov multiple correlation (mc^2) [50]. These last two coefficients reflect the relatedness of each dependent variable with the model's linear prediction (in nonrecursive models, mc^2 is computed to avoid the problem of obtaining inconsistent negative multiple correlations).

3. Results

3.1. Sociodemographic and Clinical Variables and Prevalence of VG. There were 121 non-VGU participants (62.7%, 95%CI: 55.7%–69.2%), 43 video game users (VGU) (22.3%, 95%CI: 17.0%–28.7%), and 29 video game addicts (VGA) (15.0%, 95%CI: 10.7%–20.7%). Table 1 includes the descriptive data of the total sample and the separate groups based on the video game questionnaire total raw scores. Statistical differences emerged for patients' age (with non-VGU patients being older) and the age of onset of the GD problem (with non-VGU patients also presenting older ages of onset).

There was insufficient evidence to conclude that mean VDT total scores differed according to participants' sex,

Table 2: Comparison for SOGS scores and DSM-IV criteria.

	[1]Non-VGU	[1]VGU	[1]VGA	Group	LT	QT	Effect size		
	$n = 121$	$n = 43$	$n = 29$	P	P	P	[2]Cohen's $\|d\|$		
(1a) Card games; %	27.35%	33.33%	52.17%	0.064	**0.022**	0.547	0.13	**0.52***	0.39
(1b) Horse racing; %	3.42%	0%	0%	0.338	0.998	0.999	0.27	0.27	—
(1c) Sports events; %	3.42%	7.69%	0%	0.287	0.998	0.998	0.19	0.27	0.41
(1d) Lottery/scratchcards; %	84.62%	84.62%	91.30%	0.697	0.409	0.585	0.00	0.21	0.21
(1e) Casino; %	24.79%	41.03%	26.09%	0.145	0.895	0.087	0.35	0.03	0.32
(1f) Bingo; %	51.28%	46.15%	47.83%	0.841	0.762	0.729	0.10	0.07	0.03
(1g) Stock market; %	5.13%	5.13%	0%	0.539	0.998	0.998	0.00	0.33	0.33
(1h) Slot machines; %	81.20%	89.74%	100%	**0.045**	0.998	0.998	0.24	**0.68***	0.48
(1i) Other forms of gambling; %	15.38%	5.26%	31.82%	**0.022**	0.072	**0.032**	0.34	0.39	0.73
(2) Amount of money spent: ≥300 euros; %	53.85%	66.67%	52.17%	0.341	0.883	0.162	0.26	0.03	0.30
(3) Family history of gambling; %	22.22%	15.38%	34.78%	0.208	0.204	0.132	0.18	0.28	0.46
(4) Going back to win back lost money; %	91.38%	89.74%	100%	0.307	0.998	0.998	0.06	0.43	0.48
(5) Claiming to be winning when losing; %	40.87%	43.59%	56.52%	0.385	0.171	0.607	0.06	0.32	0.26
(6) Problem recognition; %	97.44%	97.44%	100%	0.740	0.998	0.998	0.00	0.23	0.23
(7) Gambling more than planned; %	91.38%	92.31%	100%	0.347	0.998	0.998	0.03	0.43	0.41
(8) Being criticized; %	66.09%	74.36%	82.61%	0.230	0.127	0.919	0.18	0.39	0.20
(9) Feeling guilty; %	95.73%	100%	100%	0.256	0.998	0.999	0.30	0.30	—
(10) Inability to stop gambling; %	92.24%	92.31%	100%	0.385	0.998	0.998	0.00	0.41	0.41
(11) Hiding signs of gambling; %	69.83%	74.36%	78.26%	0.662	0.417	0.992	0.10	0.19	0.09
(12) Arguments with family/friends; %	78.63%	79.49%	91.30%	0.369	0.175	0.394	0.02	0.36	0.34
(13) Arguments and fights; %	74.53%	71.43%	73.91%	0.937	0.951	0.757	0.07	0.01	0.06
(14) Borrowing money and failing to return it; %	46.15%	41.03%	52.17%	0.691	0.598	0.408	0.10	0.12	0.22
(15) Skipping work due to gambling; %	43.59%	46.15%	65.22%	0.163	0.062	0.396	0.05	0.44	0.39
(16a) Taking money from home; %	77.78%	77.27%	93.33%	0.375	0.199	0.330	0.01	0.45	0.47
(16b) Taking money from partner; %	59.52%	60.00%	83.33%	0.300	0.143	0.379	0.01	**0.55***	0.54
(16c) Taking money from family; %	77.08%	86.96%	87.50%	0.541	0.514	0.704	0.26	0.28	0.02
(16d) Borrowing from banks; %	81.48%	77.78%	83.33%	0.918	0.880	0.679	0.09	0.05	0.14
(16e) Using credit cards; %	77.78%	91.67%	84.62%	0.323	0.589	0.279	0.39	0.18	0.22
(16f) Borrowing from money lenders; %	30.30%	45.45%	0%	0.239	0.999	0.999	0.32	**0.93***	**1.29***
(16g) Money from sale of shares or other bank assets; %	7.69%	14.29%	25.00%	0.553	0.311	1.000	0.21	0.48	0.27
(16h) Money from property sales; %	41.67%	50.00%	20.00%	0.552	0.369	0.348	0.17	0.48	**0.66***
(16i) Money from making out false checks; %	8.00%	0%	0%	0.654	0.999	1.000	0.42	0.42	—
SOGS: total score; mean (SD)	9.66 (3.2)	10.1 (3.6)	11.2 (2.4)	0.117	**0.043**	0.670	0.13	**0.54***	0.36
DSM1. Preoccupations with gambling; %	73.95%	80.95%	86.96%	0.318	0.191	0.964	0.17	0.33	0.16
DSM2. Need to bet more money; %	62.18%	42.86%	86.96%	**0.002**	**0.031**	**0.001**	0.39	**0.59***	**1.04***
DSM3. Unsuccessful efforts to control; %	90.76%	95.24%	100%	0.229	0.998	0.998	0.18	0.45	0.32
DSM4. Restless, irritable when not gambling; %	59.66%	71.43%	73.91%	0.227	0.203	0.639	0.25	0.31	0.06
DSM5. Gambling to escape from problems; %	73.95%	64.29%	82.61%	0.255	0.382	0.102	0.21	0.21	0.42
DSM6. Gambling again after losing money; %	73.95%	80.95%	95.65%	0.062	**0.050**	0.342	0.17	**0.63***	0.47
DSM7. Lying to family members or others; %	90.76%	95.24%	86.96%	0.494	0.578	0.260	0.18	0.12	0.29
DSM8. Committing illegal acts; %	27.73%	28.57%	30.43%	0.965	0.792	0.955	0.02	0.06	0.04
DSM9. Losing a significant relationship, job,. . .; %	78.99%	80.95%	91.30%	0.387	0.184	0.478	0.05	0.35	0.30
DSM10. Relying on others to provide money; %	70.59%	83.33%	69.57%	0.250	0.922	0.116	0.31	0.02	0.33
DSM. Total criteria; mean (SD)	7.03 (2.3)	7.24 (1.9)	8.04 (1.5)	0.114	**0.038**	0.471	0.10	**0.52***	0.47

SD: standard deviation. [1]Non-VGU (non-video game users) (total VDT score of 0); VGU: video game users (total VDT score between 1 and 19); VGA: video game addicts (total VDT score of 20 or higher). LT: linear trend; QT: quadratic trend. [2]Cohen's $|d|$ for the comparisons: non-VGU versus VGU; non-VGU versus VGA; VGU versus VGA. *Bold: moderate ($|d| > 0.50$) to high ($|d| > 0.80$) effect size.

Table 3: Comparison for clinical outcomes.

	[1]Non-VGU		[1]VGU		[1]VGA		ANOVA					
	$n = 121$		$n = 43$		$n = 29$		Group	Trends		Effect size		
	Mean	SD	Mean	SD	Mean	SD	P	LT	QT	[2]Cohen's $\lvert d \rvert$		
SCL-90: somatization	1.13	0.87	0.95	0.91	1.69	1.09	**0.003**	**0.030**	**0.008**	0.20	**0.57***	**0.74***
SCL-90: obsessive/compulsive	1.20	0.88	1.12	0.78	1.96	0.93	**<0.001**	**0.001**	**0.005**	0.10	**0.84***	**0.98***
SCL-90: interpersonal sensitivity	1.18	0.94	1.05	0.87	1.89	0.94	**<0.001**	**0.004**	**0.006**	0.14	**0.76***	**0.93***
SCL-90: depression	1.66	0.96	1.56	0.92	2.21	0.93	**0.010**	**0.026**	**0.036**	0.11	**0.58***	**0.70***
SCL-90: anxiety	1.15	0.86	1.03	0.83	1.74	0.97	**0.002**	**0.011**	**0.013**	0.14	**0.64***	**0.79***
SCL-90: hostility	1.00	0.88	0.80	0.76	1.67	1.08	**<0.001**	**0.007**	**0.002**	0.24	**0.68***	**0.93***
SCL-90: phobic anxiety	0.53	0.70	0.43	0.76	0.99	0.96	**0.007**	**0.027**	**0.023**	0.14	**0.55***	**0.65***
SCL-90: paranoia	1.02	0.84	0.98	0.78	1.77	0.96	**<0.001**	**<0.001**	**0.010**	0.05	**0.83***	**0.90***
SCL-90: psychoticism	1.06	0.80	0.89	0.75	1.58	1.03	**0.002**	**0.027**	**0.007**	0.22	**0.56***	**0.77***
SCL-90: GSI score	1.18	0.76	1.06	0.72	1.79	0.87	**<0.001**	**0.004**	**0.003**	0.16	**0.75***	**0.91***
SCL-90: PST score	49.43	21.25	48.90	21.45	65.07	18.88	**<0.001**	**0.002**	**0.035**	0.02	**0.78***	**0.80***
SCL-90: PSDI score	1.99	0.64	1.80	0.56	2.34	0.64	**0.002**	**0.007**	**0.002**	0.32	**0.55***	**0.90***
TCI-R: novelty seeking	108.36	12.21	108.51	12.92	110.22	12.39	0.778	0.529	0.744	0.01	0.15	0.14
TCI-R: harm avoidance	104.03	15.93	98.90	20.80	106.52	16.46	0.157	0.996	0.054	0.28	0.15	0.41
TCI-R: reward dependence	98.92	13.70	101.62	10.23	98.11	13.97	0.466	0.883	0.220	0.22	0.06	0.29
TCI-R: persistence	103.54	23.10	114.79	21.65	112.89	23.13	**0.012**	**0.010**	0.135	**0.50***	0.40	0.08
TCI-R: self-directedness	131.27	20.93	132.77	21.02	117.56	18.56	**0.005**	**0.012**	**0.037**	0.07	**0.69***	**0.77***
TCI-R: cooperativeness	132.95	16.40	132.69	15.48	125.78	15.23	0.107	0.068	0.282	0.02	0.45	0.45
TCI-R: self- transcendence	62.79	15.35	60.69	12.82	66.89	17.14	0.261	0.410	0.156	0.15	0.25	0.41
VG: total score	0.00	0.00	6.77	4.60	44.24	22.60	**<0.001**	**<0.001**	**<0.001**	**2.08***	**2.77***	**2.30***

SD: standard deviation. LT: linear trend; QT: quadratic trend.
[1]Non-VGU (non-video game users) (total VDT score of 0); VGU: video game users (total VDT score between 1 and 19); VGA: video game addicts (total VDT score of 20 or higher).
[2]Cohen's $\lvert d \rvert$ for the comparisons: non-VGU versus VGU; non-VGU versus VGA; VGU versus VGA. *Bold: moderate ($\lvert d \rvert > 0.50$) to high ($\lvert d \rvert > 0.80$) effect size.

employment status, marital status, use of tobacco, and use of substances.

3.2. Comparison between VG Groups for the GD Measures: SOGS and DSM-IV Questionnaires. The upper part of Table 2 shows the comparison of the SOGS scores (for each item and for the total score) between VG groups. The prevalence of patients who reported playing slot machines and other betting games was higher in the VGA group ($P = 0.045$ and $P = 0.022$). A positive linear trend was found for "playing cards" (the higher the VG level, the higher the prevalence of patients reporting this form of gambling) and a quadratic trend for the prevalence of other forms of betting (prevalences were 15.4, 5.3, and 31.8 for non-VGU, VGU, and VGA, resp.). The mean SOGS-total score presented a positive linear trend with the VG level (this means that it increased from 9.7 for non-VGU to 10.1 to VGU and 11.2 to VGA, $P = 0.043$).

According to the DSM-IV questionnaire results (lower part of Table 2), the VGA had a statistically higher prevalence of patients reporting the presence of criterion A2 ("needs to bet more money," $P = 0.002$), and linear and quadratic trends were found for this symptom. A positive linear trend was found for criterion A6 ("gambles again after losing," $P = 0.050$) and for the means for the DSM-total criteria ($P = 0.038$).

Effect size measured through Cohen's d showed that for the dichotomous SOGS-items and DSM-criteria the highest differences were between non-VGU and VGA patients (within the moderate range for significant group comparisons, except for the item "other forms of gambling" and the criterion "needs to gamble more money") and the lowest between VGU and VGA patients. Differences between non-VGA and VGA achieved moderate effect sizes for the SOGS-total score and the DSM-total criteria, and the other pairwise comparison achieved a low effect size.

3.3. Comparison between VG Groups for General Psychopathology and Personality. Table 3 shows the results of the ANOVA procedures comparing the SCL-90-R and the TCI-R mean scores between the three VG groups. All the SCL-90-R scales achieved significantly different means between the three groups. The significant linear trends obtained in the polynomial contrasts indicated that the higher the VG scores, the higher the SCL-90-R mean score (VGA > VGU > non-VGU). The additional significant quadratic trend indicated that while the mean differences between non-VGU and VGU were low, the differences between VGU and VGA were high. Cohen's d measuring the effect size for pairwise SCL-90-R and TCI-R comparisons showed that differences between non-VGU and VGU were low (except for TCI-R persistence score). Pairwise differences for the rest of the SCL-90-R scales

Table 4: Partial correlations, adjusted for participants' sex and age, between VG total score and clinical outcomes.

SCL-90: somatization	**0.248**
SCL-90: obsessive/compulsive	**0.295**
SCL-90: interpersonal sensitivity	**0.291**
SCL-90: depression	**0.221**
SCL-90: anxiety	**0.258**
SCL-90: hostility	**0.274**
SCL-90: phobic anxiety	**0.270**
SCL-90: paranoid ideation	**0.319**
SCL-90: psychoticism	**0.245**
SCL-90: GSI score	**0.297**
SCL-90: PST score	**0.266**
SCL-90: PSDI score	**0.227**
TCI-R: novelty seeking	0.085
TCI-R: harm avoidance	0.089
TCI-R: reward dependence	−0.055
TCI-R: persistence	0.091
TCI-R: self-directedness	**−0.195**
TCI-R: cooperativeness	−0.104
TCI-R: self-transcendence	0.118

Bold: significant correlation (.05 level).

obtained moderate to high effect sizes. For TCI-R scores, moderate differences were obtained for the self-directedness score for the pairwise comparison between VGA patients and the other two VG levels.

A positive linear trend was also obtained for the relationship between the VG groups and the TCI-R mean score for persistence and a negative linear trend between the VG groups and the TCI-R mean scores for self-directedness. An additional quadratic trend for TCI-R self-directedness again showed low mean differences between non-VGU and VGU and higher mean differences between VGU and VGA.

3.4. Association between VG Scores and Clinical Outcomes. Partial correlations adjusted for the covariates patients' sex and age showed that VG total scores correlated positively with all the SCL-90-R scores and negatively with the TCI-R self-directedness score (Table 4). The effect sizes of the correlations were in the moderate range.

3.5. Predictive Capacity of the Sociodemographic and the Personality Traits among VG Groups. The first stepwise linear regression included in Table 5 contains the best predictive model selected for the VG total score, considering the sociodemographic variables and the personality profile measured via the TCI-R questionnaire as independent variables. The only significant predictor was the TCI-R self-directedness score: the lower the TCI-R self-directedness score was, the higher the VG total score was.

The second model in Table 5 corresponds to the stepwise binary logistic regression evaluating the best predictors (entering in the model the same set of independent variables as in the previous multiple regression) of a score higher than

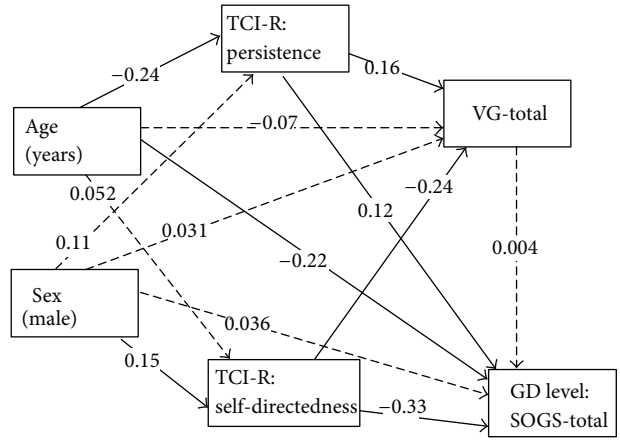

Figure 1: Structural equation model (SEM) valuing the pathways for the video game (VG) and the gambling disorder (GD) levels. Dashed lines indicate nonsignificant associations.

0 on the VG total scale (the dependent variable was coded 0 for non-VGU patients and 1 for VGU and VGA patients). Results showed that a greater likelihood of a VG above 0 (VGU and VGA) was associated with younger age and high TCI-R persistence scores.

The third model in Table 5 contains the best model for discriminating a VG total score above 20 (the dependent variable was coded 0 for non-VGU and VGU patients and 1 for VGA patients). The results showed that low TCI-R self-directedness scores increased the risk of VGA.

3.6. Pathways of the VG Level and GD Behavior. Figure 1 shows the diagram for the SEM that assesses the pathways for the outcomes VG behavior severity (measured through the VG total score) and severity of the GD (SOGS total score). Table 6 includes the statistics for the standardized coefficients of this model. The variables included in the SEM were selected from the results obtained in the previous stepwise regression models, which identified patients' age and TCI-R persistence and self-directedness scores as the most relevant predictors for VG (sex was also included as an independent variable due to its strong association with GD). The dashed lines indicate nonsignificant links. The variables selected to adjust the pathway were the ones with the highest associations in the previous analyses. The indexes measuring the model level goodness-of-fit were adequate: $\chi^2 = 0.29$ ($P = 0.589$), RMSEA = 0.01, CFI = 1, and SRMR = 0.008. The overall R^2 for the pathway was 0.16.

The VG level (measured by the VG total score) was high for patients with low TCI-R self-directedness and high TCI-R persistence scores. In addition, TCI-R trait persistence mediated the relationship between age and VG total score: younger subjects had higher TCI-R persistence scores, and a positive association was found between this personality trait and the VG score. TCI-R self-directedness also mediated the relationship between sex and VG total score. Men obtained higher scores on this personality trait, which was negatively associated with VG level.

Table 5: Predictive models for the video game questionnaire scores through step-wise regression.

Linear regression for outcome:	Predictors	B	β	P	95% CI (B)	
VG-total scale score	TCI-R: self-directedness	−0.172	−0.199	0.007	−0.296;	−0.048
Logistic regression for outcome:	Predictors	B	OR	P	95% CI (OR)	
VGU	Age (years)	−0.041	0.960	0.003	0.934;	0.986
	TCI-R: Persistence	0.016	1.016	0.033	1.001;	1.030
VGA	TCI-R: self-directedness	−0.036	0.965	0.002	0.943;	0.987

VGU: video game users (total VDT score between 1 and 19); VGA: video game addicts (total VDT score of 20 or higher).

Table 6: Structural equation model.

	Standard coefficient	SE	Z	$P > \|Z\|$	95% CI for the coefficient	
TCI-R persistence						
Sex (male)	0.1068688	0.0756534	1.41	0.0158	−0.0414092;	0.2551468
Age (years)	−0.2368213	0.0732199	−3.23	0.001	−0.3803297;	−0.0933129
_Constant	5.10091	0.4282882	11.91	<0.001	4.261481;	5.94034
TCI-R self-directedness						
Sex (male)	0.1483216	0.0773418	1.92	0.050	0.0032656;	0.2999087
Age (years)	0.0519053	0.0784299	0.66	0.508	−0.1018144;	0.2056251
_Constant	5.614348	0.5221618	10.75	<0.001	4.590929;	6.637766
VG-total score						
TCI-R persistence	0.1575215	0.0763331	2.06	0.039	0.0079114;	0.3071316
TCI-R self-directedness	−0.2375955	0.0728751	−3.26	0.001	−0.3804281;	−0.0947629
Sex (male)	0.030922	0.0768931	0.40	0.688	−0.1197858;	0.1816298
Age (years)	−0.0700488	0.0776069	−0.90	0.367	−0.2221556;	0.082058
_Constant	1.293971	0.6827771	1.90	0.058	−0.0442471;	2.63219
SOGS-total score						
TCI-R persistence	0.1196749	0.0733896	1.63	0.103	−0.0241661;	0.2635159
TCI-R self-directedness	−0.3278795	0.0694936	−4.72	0.000	−0.4640846;	−0.1916745
TDV_TOTAL	0.0034844	0.0732836	0.05	0.962	−0.1401489;	0.1471176
Sex (male)	0.0359377	0.0726224	0.49	0.621	−0.1063995;	0.1782749
Age (years)	−0.2235272	0.0713199	−3.13	0.002	−0.3633117;	−0.0837427
_Constant	5.114255	0.634818	8.06	<0.001	3.870035;	6.358476
	χ^2	P	RMSEA	CFI	SRMR	
Model level goodness-of-fit	0.291	0.589	0.01	1.00	0.008	
Equation level goodness-of-fit	Fitted	Variance	Residual	R^2	mc	mc^2
TCI-R persistence	535.6957	41.93446	493.7613	0.0782804	0.2797863	0.0782804
TCI-R self-directedness	438.6029	9.393018	429.2099	0.0214158	0.1463413	0.0214158
VG-total score	302.4843	28.20133	274.283	0.0932324	0.3053398	0.0932324
SOGS-total score	10.77644	2.064861	8.711581	0.1916088	0.4377314	0.1916088

mc = correlation between dependent variable and its prediction.
mc^2 = Bentler-Raykov squared multiple correlation coefficient.

GD severity (measured by the SOGS-total score) was not associated with VG total score, but it was associated with younger age, low TCI-R self-directedness scores, and high TCI-R persistence scores. Again, as in the case of VG, TCI-R self-directedness mediated the pathway between sex and GD level, and TCI-R persistence mediated the pathway between age and GD level.

4. Discussion

The current study assessed the prevalence of VG symptoms in a clinical sample of GD patients and explored the differences between VG groups (VGU versus VGA). Furthermore, we assessed the associations between the severity of VG symptoms and GD symptomatology, general psychopathology and

personality traits, and clinical variables and then compared them with patients without VG use (non-VGU).

The main finding of the study was that the prevalence of VGA in a consecutive clinical sample of treatment-seeking GD individuals was 15%. This is in agreement with the literature, which describes an association between the presence of gambling problems and a more frequent use of and involvement in video games [51]. Moreover, our results show that the prevalence of VG problem use or addiction among GD patients is higher than in other similar studies, which ranged from 0.6% to 10%, despite our sample being older [16, 52]. However, the rates obtained in our study are consistent with those described in an adult population [13].

The presence of VG use (VGU and VGA) was associated with specific clinical variables such as younger age, but not with GD symptomatology as measured by means of SOCS or DSM-IV criteria. Previous literature reports suggest that age and gender are strong predictors of problematic or addictive use of video games [13, 20, 51], but not of the severity of the main GD [51, 52].

The second main finding was that both VGU and VGA patients presented higher general psychopathology. This is in agreement with the existing literature [28, 53], which reports an association between a higher number of VG symptoms and depression, anxiety, and social phobia. These emotional disturbances and social problems not only may be consequences of video game addiction [16] but may also be factors that contribute to the persistence of the disorder. Indeed, Kuss [11] describes how the preference for online social relationships, the need for escapism, and use of maladaptive coping strategies to deal with daily stressors become maintaining variables. Similarly, King and Delfabbro [54] consider the problematic use of video games to be associated with attempts to achieve self-esteem or to gain social acceptance.

A third main finding was that patients who made excessive use of VG (both VGU and VGA) presented more dysfunctional personality traits, namely, lower self-directedness and higher persistence. Other studies have also found specific personality traits such as irritability/aggression, impulsivity, neuroticism, loneliness, and introversion to be associated with VGA [52, 55].

The present study has several methodological limitations that need to be taken into account. First, the participants in the sample are only representative of GD patients who seek treatment, and therefore the findings obtained may not apply to all individuals with GD. Since only 7% to 12% of GD individuals seek help for their disorder, a community sample of GD might yield different results. Second, the use of a standardized self-administered questionnaire as the assessment procedure did not allow for an in-depth evaluation of specific axis I and axis II comorbid disorders.

5. Conclusions

This study adds to the limited literature on VGA in GD clinical samples and develops a pathway model to describe the associations between VG symptoms, clinical and sociodemographic characteristics, personality traits, and general psychopathology. Based on the findings of the model, we conclude that both VGU and VGA are driven by high levels of persistence and low levels of self-directedness, and that patients tend to be male and of younger age. Intervention strategies that focus on the training of these personality features and systematic screening for potential VGU/VGA are recommended.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

[1] APA, *Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Association, Washington , DC, USA, 3rd edition, 1980.

[2] N. M. Petry and C. P. O'Brien, "Internet gaming disorder and the DSM-5," *Addiction*, vol. 108, no. 7, pp. 1186–1187, 2013.

[3] N. M. Petry, C. Blanco, R. Stinchfield, and R. Volberg, "An empirical evaluation of proposed changes for gambling diagnosis in the DSM-5," *Addiction*, vol. 108, no. 3, pp. 575–581, 2013.

[4] R. F. Leeman and M. N. Potenza, "Similarities and differences between pathological gambling and substance use disorders: a focus on impulsivity and compulsivity," *Psychopharmacology*, vol. 219, no. 2, pp. 469–490, 2012.

[5] M. N. Potenza, "How central is dopamine to pathological gambling or gambling disorder?" *Frontiers in Behavioral Neuroscience*, vol. 23, no. 7, p. 206, 2013.

[6] N. M. Petry, F. Rehbein, D. A. Gentile et al., "An international consensus for assessing internet gaming disorder using the new DSM-5 approach," *Addiction*, 2014.

[7] D. Bavelier, C. S. Green, D. H. Han, P. F. Renshaw, M. M. Merzenich, and D. A. Gentile, "Brains on video games," *Nature Reviews Neuroscience*, vol. 12, no. 12, pp. X763–X768, 2011.

[8] D. H. Han, N. Bolo, M. A. Daniels, L. Arenella, I. K. Lyoo, and P. F. Renshaw, "Brain activity and desire for Internet video game play," *Comprehensive Psychiatry*, vol. 52, no. 1, pp. 88–95, 2011.

[9] C.-H. Ko, J.-Y. Yen, S.-H. Chen, P.-W. Wang, C.-S. Chenb, and C.-F. Yen, " Evaluation of the diagnostic criteria of Internet gaming disorder in the DSM-5 among young adults in Taiwan," *Journal of Psychiatric Research*, vol. 53, pp. 103–110, 2014.

[10] H. Cho, M. Kwon, J.-H. Choi et al., "Development of the internet addiction scale based on the internet gaming disorder criteria suggested in DSM-5," *Addictive Behaviors*, vol. 39, no. 9, pp. 1361–1366, 2014.

[11] D. J. Kuss, "Internet gaming addiction: current perspectives," *Psychology Research and Behavior Management*, vol. 6, pp. 125–137, 2013.

[12] V. Anand, "A study of time management: the correlation between video game usage and academic performance markers," *Cyberpsychology and Behavior*, vol. 10, no. 4, pp. 552–559, 2007.

[13] S. Achab, M. Nicolier, F. Mauny et al., "Massively multiplayer online role-playing games: comparing characteristics of addict vs non-addict online recruited gamers in a French adult population," *BMC Psychiatry*, vol. 11, article 144, 2011.

[14] R. Festl, M. Scharkow, and T. Quandt, "Problematic computer game use among adolescents, younger and older adults," *Addiction*, vol. 108, no. 3, pp. 592–599, 2013.

[15] M. C. Haagsma, M. E. Pieterse, and O. Peters, "The prevalence of problematic video gamers in the netherlands," *Cyberpsychology, Behavior, and Social Networking*, vol. 15, no. 3, pp. 162–168, 2012.

[16] R. A. Mentzoni, G. S. Brunborg, H. Molde et al., "Problematic video game use: Estimated prevalence and associations with mental and physical health," *Cyberpsychology, Behavior, and Social Networking*, vol. 14, no. 10, pp. 591–596, 2011.

[17] APA, *Diagnostic and Statistical Manual of Mental Disorders: Text Revision*, American Psychiatric Association, Washington, DC, USA, 4th edition, 2000.

[18] D. L. King, M. C. Haagsma, P. H. Delfabbro, M. Gradisar, and M. D. Griffiths, "Toward a consensus definition of pathological video-gaming: a systematic review of psychometric assessment tools," *Clinical Psychology Review*, vol. 33, no. 3, pp. 331–342, 2013.

[19] M. D. Griffiths, "Non-addictive psychoactive drug use: implications for behavioral addiction," *Behavioral and Brain Sciences*, vol. 34, no. 6, pp. 315–316, 2011.

[20] M. D. Griffiths and A. Meredith, "Videogame addiction and its treatment," *Journal of Contemporary Psychotherapy*, vol. 39, no. 4, pp. 247–253, 2009.

[21] J. E. Grant and S. R. Chamberlain, "Gambling disorder and its relationship with substance use disorders: Implications for nosological revisions and treatment," *The American Journal on Addictions*, 2013.

[22] A. Johansson, J. E. Grant, S. W. Kim, B. L. Odlaug, and K. G. Götestam, "Risk factors for problematic gambling: a critical literature review," *Journal of Gambling Studies*, vol. 25, no. 1, pp. 67–92, 2009.

[23] R. C. Kessler, I. Hwang, R. Labrie et al., "DSM-IV pathological gambling in the National Comorbidity Survey Replication," *Psychological Medicine*, vol. 38, no. 9, pp. 1351–1360, 2008.

[24] E. M. Álvarez-Moya, S. Jiménez-Murcia, R. Granero et al., "Comparison of personality risk factors in bulimia nervosa and pathological gambling," *Comprehensive Psychiatry*, vol. 48, no. 5, pp. 452–457, 2007.

[25] L. Janiri, G. Martinotti, T. Dario, F. Schifano, and P. Bria, "The gamblers' temperament and character inventory (TCI) personality profile," *Substance Use & Misuse*, vol. 42, no. 6, pp. 975–984, 2007.

[26] D. T. Barry, E. A. Stefanovics, R. A. Desai, and M. N. Potenza, "Differences in the associations between gambling problem severity and psychiatric disorders among black and white adults: findings from the national epidemiologic survey on alcohol and related conditions," *American Journal on Addictions*, vol. 20, no. 1, pp. 69–77, 2011.

[27] N. A. Dowling and M. Brown, "Commonalities in the psychological factors associated with problem gambling and internet dependence," *Cyberpsychology, Behavior, and Social Networking*, vol. 13, no. 4, pp. 437–441, 2010.

[28] F. Tonioni, M. Mazza, G. Autullo et al., "Is Internet addiction a psychopathological condition distinct from pathological gambling?" *Addictive Behaviors*, vol. 39, no. 6, pp. 1052–1056, 2014.

[29] K. W. Muller, M. E. Beutel, B. Egloff, and K. Wölfling, "Investigating risk factors for internet gaming disorder: a comparison of patients with addictive gaming, pathological gamblers and healthy controls regarding the big five personality traits," *European Addiction Research*, vol. 20, no. 3, pp. 129–136, 2014.

[30] R. Stinchfield, "Reliability, validity, and classification accuracy of a measure of DSM-IV diagnostic criteria for pathological gambling," *The American Journal of Psychiatry*, vol. 160, no. 1, pp. 180–182, 2003.

[31] S. Jimenez-Murcia, R. Stinchfield, E. Alvarez-Moya et al., "Reliability, validity, and classification accuracy of a spanish translation of a measure of DSM-IV diagnostic criteria for pathological gambling," *Journal of Gambling Studies*, vol. 25, no. 1, pp. 93–104, 2009.

[32] B. W. Brown and K. Russell, "Methods of correcting for multiple testing: operating characteristics," *Statistics in Medicine*, vol. 16, no. 22, pp. 2511–2528, 1997.

[33] H. R. Lesieur and S. B. Blume, "The south oaks gambling screen (SOGS): a new instrument for the identification of pathological gamblers," *The American Journal of Psychiatry*, vol. 144, no. 9, pp. 1184–1188, 1987.

[34] M. Chóliz and C. Marco, "Patrón de uso y dependencia de videojuegos en infancia y adolescencia," *Anales de Psicología*, vol. 27, no. 2, pp. 418–426, 2011.

[35] L. R. Derogatis, *SCL-90-R: Cuestionario de 90 Síntomas: Manual*, TEA Editorial, Madrid, Spain, 2002.

[36] C. R. Cloninger, *The Temperament and Character Inventory—Revised*, Center for Psychobiology of Personality, Washington University, St. Louis, Mo, USA, 1999.

[37] APA, *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, American Psychiatric Association, Washington, Wash, USA, 5th edition, 2013.

[38] APA, *Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Association, Washington, DC, USA, 3rd edition, 1987.

[39] E. Echeburúa, C. Baéz, J. Fernández-Montalvo, and D. Páez, "Cuestionario de Juego Patológico de South Oaks (SOGS): validación española. [South Oaks Gambling Screen (SOGS): Spanish validation]," *Analisis y Modificación de Conducta*, vol. 20, no. 74, pp. 769–791, 1994.

[40] R. Stinchfield, "Reliability, validity, and classification accuracy of the South Oaks Gambling Screen (SOGS)," *Addictive Behaviors*, vol. 27, no. 1, pp. 1–19, 2002.

[41] S. M. Alessi and N. M. Petry, "Pathological gambling severity is associated with impulsivity in a delay discounting procedure," *Behavioural Processes*, vol. 64, no. 3, pp. 345–354, 2003.

[42] D. R. Strong, S. B. Daughters, C. W. Lejuez, and R. B. Breen, "Using the Rasch model to develop a revised gambling attitudes and beliefs scale (GABS) for use with male college student gamblers," *Substance Use and Misuse*, vol. 39, no. 6, pp. 1013–1024, 2004.

[43] APA, *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, American Psychiatric Association, Washington, DC, USA, 4th edition, 1994.

[44] C. R. Cloninger, D. M. Svrakic, and T. R. Przybeck, "A psychobiological model of temperament and character," *Archives of General Psychiatry*, vol. 50, no. 12, pp. 975–990, 1993.

[45] F. Gutiérrez, N. Torrens, T. Boget et al., "Psychometric properties of the Temperament and Character Inventory (TCI) questionnaire in a Spanish psychiatric population," *Acta Psychiatrica Scandinavica*, vol. 103, no. 2, pp. 143–147, 2001.

[46] J. A. Gutiérrez-Zotes, C. Bayón, C. Montserrat et al., "Temperament and Character Inventory Revised (TCI-R). Standardization and normative data in a general population sample," *Actas Espanolas de Psiquiatria*, vol. 32, no. 1, pp. 8–15, 2004.

[47] O. Martínez-Azumendi, C. Fernández-Gómez, and M. Beitia-Fernández, "Factorial variance of the SCL-90-R in a Spanish out-patient psychiatric sample," *Actas Espanolas de Psiquiatria*, vol. 29, no. 2, pp. 95–102, 2001.

[48] S. Jiménez-Murcia, E. M. Álvarez-Moya, R. Granero et al., "Cognitive-behavioral group treatment for pathological gambling: analysis of effectiveness and predictors of therapy outcome," *Psychotherapy Research*, vol. 17, no. 5, pp. 544–552, 2007.

[49] R. B. Kline, *Principles and Practice of Structural Equation Modeling*, Guilford Press, New York, NY, USA, 3rd edition, 2010.

[50] P. M. Bentler and T. Raykov, "On measures of explained variance in nonrecursive structural equation models," *Journal of Applied Psychology*, vol. 85, no. 1, pp. 125–131, 2000.

[51] K. Dunn, P. Delfabbro, and P. Harvey, "A preliminary, qualitative exploration of the influences associated with drop-out from cognitive-behavioural therapy for problem gambling: an Australian perspective," *Journal of Gambling Studies*, vol. 28, no. 2, pp. 253–272, 2012.

[52] B. Walther, M. Morgenstern, and R. Hanewinkel, "Co-occurrence of addictive behaviours: personality factors related to substance use, gambling and computer gaming," *European Addiction Research*, vol. 18, no. 4, pp. 167–174, 2012.

[53] D. J. Kuss, M. D. Griffiths, L. Karila, and J. Billieux, "Internet addiction: a systematic review of epidemiological research for the last decade," *Current Pharmaceutical Design*, vol. 20, no. 25, pp. 4026–4052, 2014.

[54] D. L. King and P. H. Delfabbro, " Internet gaming disorder treatment: a review of definitions of diagnosis and treatment outcome," *Journal of Clinical Psychology*, 2014.

[55] M. Mehroof and M. D. Griffiths, "Online gaming addiction: the role of sensation seeking, self-control, neuroticism, aggression, state anxiety, and trait anxiety," *Cyberpsychology, Behavior, and Social Networking*, vol. 13, no. 3, pp. 313–316, 2010.

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Research Article

Adult Separation Anxiety and TCI-R Personality Dimensions in Patients with Anxiety, Alcohol Use, and Gambling: A Preliminary Report

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Background. Nowadays, adult separation anxiety disorder (ASAD) is an established diagnostic category but is little investigated in subjects with addictive behaviours. *Objective*. To assess the presence of ASAD among patients with addictive disorders in comparison with anxiety patients and measure the personality correlates in all these groups. *Methods*. 103 outpatients, meeting DSM-IV-TR criteria for anxiety disorders (38 patients), alcohol dependence (30 patients), or pathological gambling (35 patients), were assessed by the Structured Clinical Interview for Separation Anxiety Symptoms (SCI-SAS) and the Adult Separation Anxiety Checklist (ASA-27) for separation anxiety and by the Temperament and Character Inventory-Revised (TCI-R) for personality characteristics. *Results*. ASAD is detected in 34.2% of anxiety patients, 13.3% of alcoholics, and 11.4% of gamblers. Separation anxiety scores correlate positively with harm avoidance and negatively with self-directedness in all groups; further correlations are seen among addictive patients only, that is, self-transcendence for gamblers and cooperativeness for both alcoholics and gamblers. *Conclusions*. The prevalence of ASAD is lower among addictive patients than in those with anxiety disorders; correlations are found between separation anxiety and specific TCI-R dimensions, with some matching across the three diagnostic groups.

1. Introduction

Separation anxiety can be defined as a condition burdened by an excessive and inappropriate display of fear and distress when the individual is faced with situations of separation from home or from a specific attachment figure. As is well known, the discomfort arisen by the separation from an attachment figure is related to the ordinary childhood development [1, 2], with a probable evolutionary purpose: the retention of the human offspring, still inept, near its main caregiver [3].

Only if the sensitivity to the separation becomes excessive and prolonged, with intense anxiety and interference in daily life activities or normal development, it can be diagnosed as separation anxiety disorder (SAD).

Although this disorder has been classically defined as a childhood phenomenon, growing evidence exists that separation anxiety may have an adult onset (adult separation anxiety disorder, ASAD), regardless of history of childhood separation anxiety disorder (CSAD) [4].

Many studies have been conducted to evaluate the clinical and epidemiological characteristics of this disease [5, 6], the prevalence and gender differences [7], the impairment of functioning [5], the correlation with specific biomarkers [8, 9], and the temperament and character dimensions [10].

Apart from general population studies [5], the ASAD comorbidity has been investigated mainly in patients with mood disorders [11], anxiety disorders [7], posttraumatic stress disorder [12], and personality disorders [4, 7].

Recently, the American Psychiatric Association, in its DSM-5, decided to create a brand new specific ASAD category within the general section of the anxiety disorders [13].

Apart of the seminal study of Loas et al. [14], to the best of our knowledge, no clinical study has further investigated the presence of ASAD among patients with addictive disorders, with particular reference to gambling.

The objective of this study is to assess the presence of adult separation anxiety in patients with chemical or behavioral addictions, in comparison with a clinical sample of anxiety patients, and to measure the personality correlates in all the groups using the Temperament and Character Inventory-Revised (TCI-R) [15].

2. Materials and Methods

2.1. Participants. Subjects were recruited, during the year 2012 and in a consecutive manner, among clients referring to the adult psychiatric outpatient clinic of the "A. Gemelli" University General Hospital in Rome.

Inclusion criteria were (1) currently meeting DSM- IV-TR [16] criteria for anxiety disorder (38 patients), alcohol dependence (30 patients), or pathological gambling (35 patients); (2) having an age of 18 to 65 years; (3) for the anxious patients, spending at least one month of integrated treatments including benzodiazepines and/or selective serotonin reuptake inhibitors-serotonin norepinephrine reuptake inhibitors (SSRI-SNRI); (4) for the alcoholics and gamblers, spending at least one month of a specific rehabilitation program requiring total abstinence from the addictive behavior (alcohol abuse or pathological gambling) and the possibility, upon the clinician's advice, of a maintenance treatment with mood stabilizers (valproate, gabapentin, and pregabalin).

Subjects were excluded if any of the following conditions were present: (1) a diagnosis of mental retardation or documented IQ < 70; (2) any other current axis I DSM-IV-TR diagnosis; (3) unstable general medical conditions; (4) clinically significant prestudy physical exam, electrocardiogram, laboratory, or urinalysis abnormalities indicating serious medical disease impairing evaluation; (5) pregnant or breast-feeding women; (6) recent use of not prescribed drugs.

2.2. Procedures. DSM-IV-TR current diagnosis was preliminarily established by trained psychiatrists (G. P. and A. B.). Then an anamnestic interview was administered in order to obtain sociodemographic information and psychiatric history.

All participants were interviewed by specifically trained interviewers (M. P., P. G., and A. D. A.) using the Structured Clinical Interview for Separation Anxiety Symptoms (SCI-SAS) [17] and the Adult Separation Anxiety Checklist (ASA-27) [18].

Moreover they were administered the TCI-R, the Italian version [19, 20].

The study was conducted in accordance with the latest revision of the Declaration of Helsinki and the rules of Good Clinical Practice (ICH-GCP): all subjects provided written informed consent after a complete description of the study procedures and participated without receiving any form of payment. In order to ensure anonymity all the acquired data were deidentified before any further manipulation, ensuring an adequate level of protection, using a double level of data encryption.

2.3. Separation Anxiety Assessment. The categorical assessment of CSAD and ASAD was conducted using the SCI-SAS [17]. This semistructured interview contains items derived from the DSM-IV-TR criteria for CSAD with symptoms modified for adulthood. According to the DSM-IV, endorsement of three or more of the eight criterion symptoms was used as a threshold to determine a diagnosis of CSAD and of ASAD. For the diagnosis were required a symptom duration of at least 4 weeks and clinically significant distress or impairment in social, academic, occupational, or other important areas of functioning.

The dimensional measure of ASAD was performed by administering a self-report questionnaire, the ASA-27 [18]. The ASA-27 is a 27-item inventory which rates symptoms of adult separation anxiety after the age of 18, having high levels of internal consistency (Cronbach's $\alpha = 0.89$) and test-retest reliability ($r = 0.86$; $P < 0.001$); moreover it has shown concurrent validity with clinical assessments of ASAD, with a cut-off score of twenty-two.

2.4. Personality Assessment. Personality was investigated by means of the TCI-R [20]. This is a 240-item, five-point Likert scale, a reliable and valid questionnaire that measures seven dimensions of personality: four dimensions of temperament (i.e. harm avoidance (HA), novelty seeking (NS), reward dependence (RD), and persistence (P)) and three character traits (i.e. self-directedness (SD), cooperativeness (CO), and self-transcendence (ST)) [15]. Internal consistency of the different personality dimensions in the Italian adaptation ranged between $\alpha = 0.78$ and $\alpha = 0.89$ [8].

2.5. Statistical Analysis. Statistical analysis was conducted using SPSS for Windows, Version 15 (SPSS Inc., Chicago, Illinois). Dichotomous data were compared by chi-square test using the Fisher or the Yates corrections as appropriate. Continuous data were expressed as means ± standard deviation and compared by one-way ANOVA. The principal outcome analysis consisted of nonparametric Kruskal-Wallis H test for comparison between the three groups. Spearman's rank correlation coefficient was employed to examine the relationship between continuous variables. All tests were 2-tailed, with statistical significance set at $P < 0.05$.

3. Results

The study group included 38 patients with anxiety disorders (mostly generalized anxiety disorder and panic disorder), 30 patients with an alcohol use disorder (mostly alcohol dependence), and 35 patients with a gambling disorder (i.e., pathological gambling). The demographic characteristics are summarized in Table 1.

Separation Anxiety in the Three Study Groups. No statistically significant difference was found in the frequency of CSAD

Table 1: Demographic characteristics.

Characteristics of patients	ANX ($N = 38$)	ALC ($N = 30$)	PG ($N = 35$)
Age (mean ± SD)	39.82 ± 11.97	51.03 ± 8.68	50.63 ± 13.07
Gender			
Male	8 (21.1%)	13 (43.3%)	28 (80.0%)
Female	30 (78.9%)	17 (56.7%)	7 (20.0%)
Marital status			
Single	20 (52.6%)	15 (50.0%)	9 (25.7%)
Married	16 (42.1%)	11 (36.7%)	18 (51.4%)
Divorced/widowed	2 (5.3%)	4 (13.3%)	8 (22.9%)
Education			
Middle school	7 (18.4%)	7 (23.3%)	12 (34.3%)
High school	22 (57.9%)	15 (50.0%)	18 (51.4%)
University degree	9 (23.7%)	8 (26.7%)	5 (14.3%)
Occupation			
Employed	21 (55.3%)	13 (43.3%)	20 (57.1%)
Unemployed	3 (7.9%)	13 (43.3%)	3 (8.6%)
Other	14 (36.8%)	4 (13.3%)	12 (34.3%)

ANX: anxiety disorders; ALC: alcohol use disorders; PG: pathological gamblers.
Other: student, retired, and housewife.

Table 2: Separation anxiety across the three study groups.

	ANX ($N = 38$)	ALC ($N = 30$)	PG ($N = 35$)	P value
CSAD	8 (21.1%)	3 (10.0%)	2 (5.7%)	0.227
ASAD	13 (34.2%)	4 (13.3%)	4 (11.4%)	0.028
ASA-27 (mean value ± SD)	23.45 ± 16.75	22.50 ± 12.92	20.66 ± 12.78	0.777
ASA-27 (score ≥ 22)	17 (44.7%)	9 (30.0%)	15 (42.8%)	0.422

ANX: anxiety disorders; ALC: alcohol use disorders; PG: pathological gamblers.
CSAD: childhood separation anxiety disorder; ASAD: adult separation anxiety disorder.

across the three diagnostic groups ($P = 0.227$). As a category, ASAD is detected in about one-third of the anxiety patients in comparison to some ten percent in the other study groups ($P < 0.05$). If separation anxiety is assessed dimensionally, mean values do not differ in the three groups ($P = 0.777$). Finally, when the cut-off of ASA-27 is taken into account, the number of pathological gamblers scoring above the threshold is close to the amount found in the anxiety group (Table 2).

Correlation of Separation Anxiety Scores and Personality Dimensions. Spearman's rho correlation coefficients of the seven TCI-R main dimensions with the ASA-27 rough scores are shown in Table 3. A strong positive correlation is found between the HA and the separation anxiety symptom scores: this is statistically significant in all the three groups with a maximum in the anxiety ($P < 0.01$). Another strong correlation, albeit inverse, is found in all three groups between the SD and the ASA-27 scores, with maximum statistical significance for pathological gambling and anxiety patients ($P < 0.01$). Further correlations are seen among addictive patients only, that is, ST for gamblers ($P < 0.01$) and CO for both alcoholics ($P < 0.05$) and gamblers ($P < 0.05$).

Table 3: Correlation of ASA-27 scores with TCI-R dimensions across the three study groups (Spearman's rho).

	ANX	ALC	PG
Novelty seeking	−0.160	−0.097	−0.060
Harm avoidance	0.670**	0.384*	0.383*
Reward dependence	0.240	−0.156	0.003
Persistence	0.192	0.114	0.242
Cooperativeness	0.093	−0.395*	−0.361*
Self-directedness	−0.482**	−0.386*	−0.566**
Self-transcendence	0.144	0.088	0.436**

ANX: anxiety disorders; ALC: alcohol use disorders; PG: pathological gamblers.
*$P < 0.05$; **$P < 0.01$.

4. Discussion

With reference to study aims, the assessment of separation anxiety in the three groups showed differences in the categorical prevalence of ASAD, which was lower among alcoholics and gamblers; moreover, the scores of separation anxiety showed specific correlations with some TCI-R dimensions.

4.1. Prevalence Rates. Our data almost confirm the previous literature results. Considering the prevalence of separation anxiety in general population, the National Comorbidity Survey Replication (NCS-R) [6] showed a 12-month ASAD prevalence of 1.9% and a lifetime prevalence of 6.6% [5]; more than half of those diagnosed with ASAD had a history of mood disorders (53%), and the majority (75%) had received or were in treatment for emotional problems. Scanning the clinical studies, Pini et al. [21] reported that 42.4% of the anxiety and mood disorder outpatients screened also met the ASAD criteria. The prevalence of ASAD in dependent personality disorder patients was examined in a large patient sample with alcohol or drug addiction compared to nonpatient controls [14]: the rates in the control participants were from 2 to 5%, whilst in patients the results were significantly higher, ranging from 6 to 31%; in both cases, those with alcohol addictions had the lowest prevalence of ASAD. As reported, we found that the ASAD lifetime frequency rate is 11.4% in the gambling, 13.3% in the alcohol, and 34.2% in the anxiety sample. To the best of our knowledge, this is the first study assessing the frequency of ASAD among gamblers, so confirming that the cooccurrence of separation anxiety and addictive disorders is clearly less frequent than the cooccurrence of separation anxiety with mood or anxiety disorders.

4.2. TCI-R Measures. Many studies showed a correlation between TCI-R dimensions and anxiety disorders, gambling and alcohol addiction.

Regarding anxiety, all studies agreed on two core points: a high correlation between the temperamental dimension of harm avoidance (HA) and anxiety symptoms and an important inverse correlation between the character dimensions of self-directedness (SD) and anxiety symptoms, with HA scores increasingly higher and SD increasingly lower with the illness severity growing [22–25]. However Lu et al. [26] suggested that, although anxiety is linked to high HA scores, only high novelty seeking (NS) appears as a good predictor of anxiety; indeed in agreement with the original viewpoint by Cloninger, people with high NS can show anxiety characterized by generalized turmoil or alarm without specific premonitory cues, frequently bodily pains, and slow fatigability [27]. According to these results HA and NS would then be connected and could be the litmus paper of two different forms of anxiety.

Regarding addictive disorders, alcohol-dependent patients in general scored higher on NS and lower on SD than controls: according to the authors [28, 29] the lower SD indicates a predisposing factor for alcohol dependence, even if it could be seen as either preceding or consequent upon alcohol pathological use. Instead, pathological gamblers showed higher NS values, lower SD, and lower cooperativeness (CO) with higher NS associated with earlier age of onset of problem gambling [30–32].

The only study that measured the TCI-R dimension in ASAD reported an elevation in HA, reward dependence (RD), and self-transcendence (ST) levels and lower SD scores, with ASAD patients showing quantitatively greater severity in high HA and lower SD; the TCI-R profile of these subjects seems very similar to patients with anxiety disorders [10].

The results of our research partially confirm all these literature findings, even if there are some peculiar differences that deserve some clarification. The HA strongly correlates with separation anxiety symptoms in all the three groups: the score of this dimension indicates fear of the unknown and shyness with strangers, which could lead to avoidance behaviour especially in new situations. High levels of HA are linked to overcaution, insecurity, and passivity [15, 33]. On the contrary, NS does not correlate with separation anxiety in any of the groups, confirming that this kind of anxiety is different than that of the other anxiety disorders, as mentioned above.

Focusing on the other results, SD shows a strong inverse correlation with ASA-27 scores in all the three clinical samples. Since SD could be defined as the measure of resourcefulness and self-acceptance [34], low levels of SD are linked to irresponsibility, inefficiency, weakness, and bad self-reliance. This is consistent with a fundamental role of separation anxiety in the integration of functions of the self.

Cooperativeness seems to be inverse-correlated with ASAD symptoms only within the addictive sample, both in alcohol and gambling. Considering that CO is the capacity to understand and accept other people [15], low levels of CO are linked to intolerance, incomprehension, nonsociability, and indifference.

The ST dimension appears to be characteristic of the gamblers. ST refers to magical thinking, unselfishness, and superstition, prototypical features of a behavioural addiction [32].

5. Conclusions

This study is the first one assessing the frequency rates of ASAD in both chemical and behavioural addiction, as compared to a sample of anxiety patients. In addition we pointed out the temperament and character correlations of separation anxiety in these patients, which were shared across the disorders (HA, SD) or typical of the addictions (CO, ST). Limitations of this preliminary investigation include a small sample size, some imbalance in the demographic characteristics of the three populations, and a lack of clinical subtyping. So, our observations need to be replicated in larger groups, also widening the target on other chemical and behavioural addictions and taking into account further comorbidities.

Disclosure

No pharmaceutical and industry support was employed in this study.

Conflict of Interests

The authors declare no conflict of interests regarding the publication of this paper.

References

[1] M. D. Ainsworth, "The development of infant-mother interaction among the Ganda," in *Determinants of Infant Behavior*, B. M. Floss, Ed., John Wiley & Sons, New York, NY, USA, 1963.

[2] J. Bowlby, *Attachment and Loss, vol. 2. Separation: Anxiety and Anger*, Basic Books, New York, NY, USA, 1973.

[3] A. Bruschi, A. De Angelis, P. Grandinetti, M. Pascucci, L. Janiri, and G. Pozzi, "Separation anxiety disorder: evidence of literature and clinical implications," *Rivista di Psichiatria*, vol. 47, no. 5, pp. 355–364, 2012.

[4] V. Manicavasagar, D. Silove, J. Curtis, and R. Wagner, "Continuities of separation anxiety from early life onto adulthood," *Journal of Anxiety Disorders*, vol. 14, no. 1, pp. 1–18, 2000.

[5] M. K. Shear, R. Jin, A. M. Ruscio, E. E. Walters, and R. C. Kessler, "Prevalence and correlates of estimated DSM-IV child and adult separation anxiety disorder in the National Comorbidity Survey Replication," *The American Journal of Psychiatry*, vol. 163, no. 6, pp. 1074–1083, 2006.

[6] R. C. Kessler, P. Berglund, W. T. Chiu et al., "The US National Comorbidity Survey Replication (NCS-R): design and field procedures," *International Journal of Methods in Psychiatric Research*, vol. 13, no. 2, pp. 69–92, 2004.

[7] D. M. Silove, C. L. Marnane, R. Wagner, V. L. Manicavasagar, and S. Rees, "The prevalence and correlates of adult separation anxiety disorder in an anxiety clinic," *BMC Psychiatry*, vol. 10, article 21, pp. 1–7, 2010.

[8] B. Chelli, S. Pini, M. Abelli et al., "Platelet 18 kDa translocator protein density is reduced in depressed patients with adult separation anxiety," *European Neuropsychopharmacology*, vol. 18, no. 4, pp. 249–254, 2008.

[9] B. Costa, S. Pini, C. Martini et al., "Ala147Thr substitution in translocator protein is associated with aduit separation anxiety in patients with depression," *Psychiatric Genetics*, vol. 19, no. 2, pp. 110–111, 2009.

[10] S. Mertol and T. Alkin, "Temperament and character dimensions of patients with adult separation anxiety disorder," *Journal of Affective Disorders*, vol. 139, no. 2, pp. 199–203, 2012.

[11] S. Pini, M. Abelli, M. Mauri et al., "Clinical correlates and significance of separation anxiety in patients with bipolar disorder," *Bipolar Disorders*, vol. 7, no. 4, pp. 370–376, 2005.

[12] L. Dell'Osso, C. Carmassi, L. Musetti et al., "Lifetime mood symptoms and adult separation anxiety in patients with complicated grief and/or post-traumatic stress disorder: a preliminary report," *Psychiatry Research*, vol. 198, no. 3, pp. 436–440, 2012.

[13] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Publishing, Arlington, Va, USA, 5th edition, 2013.

[14] G. Loas, F. Atger, F. Perdereau et al., "Comorbidity of dependent personality disorder and separation anxiety disorder in addictive disorders and in healthy subjects," *Psychopathology*, vol. 35, no. 4, pp. 249–253, 2002.

[15] C. R. Cloninger, D. M. Svrakic, and T. R. Przybeck, "A psychobiological model of temperament and character," *Archives of General Psychiatry*, vol. 50, no. 12, pp. 975–990, 1993.

[16] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorder*, American Psychological Association, Washington, DC, USA, 4th edition, 1994.

[17] J. M. Cyranowski, M. K. Shear, P. Rucci et al., "Adult separation anxiety: psychometric properties of a new structured clinical interview," *Journal of Psychiatric Research*, vol. 36, no. 2, pp. 77–86, 2002.

[18] V. Manicavasagar, D. Silove, R. Wagner, and J. Drobny, "A self-report questionnaire for measuring separation anxiety in adulthood," *Comprehensive Psychiatry*, vol. 44, no. 2, pp. 146–153, 2003.

[19] G. Martinotti, L. Mandelli, M. di Nicola et al., "Psychometric characteristic of the Italian version of the Temperament and Character Inventory-Revised, personality, psychopathology, and attachment styles," *Comprehensive Psychiatry*, vol. 49, no. 5, pp. 514–522, 2008.

[20] C. R. Cloninger, *The Temperament and Character Inventory—Revised*, Center for Psychobiology of Personality, Washington University, Washington, DC, USA, 1999.

[21] S. Pini, M. Abelli, K. M. Shear et al., "Frequency and clinical correlates of adult separation anxiety in a sample of 508 outpatients with mood and anxiety disorders," *Acta Psychiatrica Scandinavica*, vol. 122, no. 1, pp. 40–46, 2010.

[22] C. R. Cloninger, A. H. Zohar, S. Hirschmann, and D. Dahan, "The psychological costs and benefits of being highly persistent: personality profiles distinguish mood disorders from anxiety disorders," *Journal of Affective Disorders*, vol. 136, no. 3, pp. 758–766, 2012.

[23] E. Nyman, J. Miettunen, N. Freimer et al., "Impact of temperament on depression and anxiety symptoms and depressive disorder in a population-based birth cohort," *Journal of Affective Disorders*, vol. 131, no. 1–3, pp. 393–397, 2011.

[24] S. Ball, J. Smolin, and A. Shekhar, "A psychobiological approach to personality: examination within anxious outpatients," *Journal of Psychiatric Research*, vol. 36, no. 2, pp. 97–103, 2002.

[25] N. Jiang, T. Sato, T. Hara, Y. Takedomi, I. Ozaki, and S. Yamada, "Correlations between trait anxiety, personality and fatigue: study based on the Temperament and Character Inventory," *Journal of Psychosomatic Research*, vol. 55, no. 6, pp. 493–500, 2003.

[26] X. Lu, Z. Chen, X. Cui et al., "Effects of temperament and character profiles on state and trait depression and anxiety: a prospective study of a Japanese youth population," *Depression Research and Treatment*, vol. 2012, Article ID 604684, 8 pages, 2012.

[27] C. R. Cloninger, "A unified biosocial theory of personality and its role in the development of anxiety states," *Psychiatric Developments*, vol. 4, no. 3, pp. 167–226, 1986.

[28] P. Basiaux, O. le Bon, M. Dramaix et al., "Temperament and character inventory (TCI) personality profile and sub-typing in alcoholic patients: a controlled study," *Alcohol and Alcoholism*, vol. 36, no. 6, pp. 584–587, 2001.

[29] O. Le Bon, P. Basiaux, E. Streel et al., "Personality profile and drug of choice; a multivariate analysis using Cloninger's TCI on heroin addicts, alcoholics, and a random population group," *Drug and Alcohol Dependence*, vol. 73, no. 2, pp. 175–182, 2004.

[30] L. Janiri, G. Martinotti, T. Dario, F. Schifano, and P. Bria, "The gamblers' Temperament and Character Inventory (TCI) personality profile," *Substance Use & Misuse*, vol. 42, no. 6, pp. 975–984, 2007.

[31] S. Jiménez-Murcia, E. M. Álvarez-Moya, R. Stinchfield et al., "Age of onset in pathological gambling: clinical, therapeutic and personality correlates," *Journal of Gambling Studies*, vol. 26, no. 2, pp. 235–248, 2010.

[32] M. Di Nicola, D. Tedeschi, M. Mazza et al., "Behavioural addictions in bipolar disorder patients: role of impulsivity and personality dimensions," *Journal of Affective Disorders*, vol. 125, no. 1–3, pp. 82–88, 2010.

[33] C. R. Cloninger, "Temperament and personality," *Current Opinion in Neurobiology*, vol. 4, no. 2, pp. 266–273, 1994.

[34] C. R. Cloninger, D. M. Svrakic, and T. R. Przybeck, "Can personality assessment predict future depression? A twelve-month follow-up of 631 subjects," *Journal of Affective Disorders*, vol. 92, no. 1, pp. 35–44, 2006.

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Research Article

Prevalence and Correlates of Binge Drinking among Young Adults Using Alcohol: A Cross-Sectional Survey

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Background. Although binge drinking prevalence and correlates among young people have been extensively studied in the USA and Northern Europe, less is known for Southern Europe countries with relatively healthier drinking cultures. *Objective*. We aimed at analyzing prevalence and correlates of binge drinking in a representative sample of young adults in Italy. *Methods*. We conducted a cross-sectional survey among alcohol-consuming young adults. We carried out univariate and multivariate analyses to assess associations between recent binge drinking and candidate variables. *Results*. We selected 654 subjects, with 590 (mean age: 20.65 ± 1.90) meeting inclusion criteria. Prevalence for recent binge drinking was 38.0%, significantly higher for females than males. Multivariate analysis showed that high alcohol expectancies, large amount of money available during the weekend, interest for parties and discos, female gender, cannabis use, influence by peers, and electronic cigarettes smoking all were significantly associated with recent binge drinking, whereas living with parents appeared a significant protective factor. *Conclusions*. More than a third of young adults using alcohol are binge drinkers, and, in contrast with findings from Anglo-Saxon countries, females show higher risk as compared with males. These data suggest the increasing importance of primary and secondary prevention programmes for binge drinking.

1. Introduction

Binge drinking can be described as heavy alcohol use over a short period of time [1], and it is typically defined by a consumption of four or five drinks in a row among women and men, respectively [2]. This dangerous pattern of alcohol consumption is highly prevalent among young adults and a public health concern in the USA [3] as well as in most of European countries [4]. Data from the 2001 National Household Survey on Drug Abuse on 19–21-year-old US adults highlighted a weekly binge drinking prevalence of 12% and 27% among females and males, respectively [5]. At the same time, relevant research shows that there is an increase of binge drinking among young people also across Europe [6, 7]. A six European countries (Germany, Iceland, Italy, Netherlands, Poland, and Scotland) cross-sectional survey on 16,551 pupils from 114 public schools showed that 27% of the sample had consumed >5 drinks in a row on at least 1 occasion in their life [8]. Pleasure, habit, increasing confidence, anxiety or stress, and social pressures have been reported as the most common reasons for alcohol drinking during adolescence and early adulthood [9]. Furthermore, the impact of binge drinking among young people has been associated with an increased risk of social and clinical consequences in the adulthood, such as illicit drug use, psychiatric morbidity, homelessness, convictions, school exclusion, lack of qualifications, and accidents [10–12]. Indeed, alcohol dependence in young adults is often preceded by higher persisting rates of frequent, intense, or binge drinking [13]. Adolescents and young adults who engage in binge drinking are more likely to report other health risk behaviors [14], such as smoking cigarettes and/or cannabis [15–18]. In a sample with a modal

age of 18 years both cigarettes and marijuana use predicted both binge drinking and an extreme level of binge drinking, defined as ≥15 drinks in a row [19]. Also, comorbid mental disorders might play a role in alcohol misuse risk [20].

However, studies on binge drinking characteristics and correlates conducted in Southern Europe are sparse [21–24], though relatively healthier drinking culture might moderate magnitude and consequences of excessive alcohol intake among young people [25]. Furthermore, there is a lack of research exploring prevalence and correlates of binge drinking in natural settings, whereas most of studies were specifically conducted among high school [14, 23] or college/university students [2, 21, 22]. With a view of remedying these limitations, the aim of this cross-sectional study was to explore prevalence and correlates of binge drinking in a representative sample of not abstemious young adults recruited in area of the Milan nightlife scene.

2. Methods

2.1. Study Design. We conducted a cross-sectional survey on young adults aged between 18 and 24 years, drawn up according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Statement - Checklist [26]. The Ethics Committee of University of Milano Bicocca approved the study.

2.2. Participants and Peer Interviewers. We consecutively recruited not abstemious young adults aged between 18 and 24 years. Those who joined the study received an information sheet and signed a written consent. We included only individuals able to sign the informed consent and excluded people who self-reported consumption of alcohol or drugs. The interviewers were students, peers aged between 18 and 24 years, selected from different Schools of Milano Bicocca University, and receiving 10 hrs training for the research project about data collection procedures, including checking eligibility, providing information on the research project, obtaining consent, and distributing and assisting with questionnaires. Questionnaires were administered through a Smartphone application. Subjects who accepted to participate to the study received a €10.00 mobile phone recharge.

2.3. Settings. Recruitment took place in urban locations of Milan nightlife scene, an area of about 1.3 million of inhabitants. We choose areas with a high density of pubs, clubs, discos, or live music events. The recruitment period was between April and July, 2013.

2.4. Measures. Recent binge drinking was assessed by a single question exploring if a consumption of four or five drinks in a row among females and males, respectively, occurred at least once, in the last two weeks. In order to analyze potential factors associated with binge drinking, we identified from scientific literature [5, 27–30] relevant candidate correlates, building a specific 10-minute questionnaire including questions on sociodemographic, clinical, individuals, and lifestyle characteristics, as well as substance and alcohol-related behaviors.

(a) Sociodemographic Characteristics. We collected information on age, gender, country of birth, living condition, relationship, educational and employment status, and financial availability for each weekend.

(b) Clinical and Individual Characteristics. As there is a strong association between substance-related behaviors and mental disorders [31–33], particularly between binge drinking and depression [34], we investigated presence of a depressive disorder with a yes/no single item screening question: *have you felt depressed or sad much of the time in the past year?* We screened for anxiety symptoms in the same manner, asking: *have you felt anxious much of the time in the past year?* Single-item questions have been used for depressive disorders screening in both general and clinical populations [35, 36], as well as for anxiety detection [37]. In order to assess impulsivity, likely associated with the risk of binge drinking among young adults [38, 39], we explored its levels using specific items of Substance Use Risk Profile Scale (SURPS) [40]. The SURPS subscale for impulsivity is a five-item questionnaire developed for use in adolescents, and it has been correlated with alcohol abuse and physiological dependence symptoms [40].

(c) Lifestyle Characteristics. First, we explored the interest for joining events and attending recreational settings where it may be easier engaging in binge drinking, such as night parties or discos [27, 41]. Second, due to the high rates of alcohol use in athlete populations [42], we checked the involvement in sport activities. Finally, we explored religiosity that, on the other hand, may represent a potential protective factor [43].

(d) Substance and Alcohol-Related Behaviors. We analyzed substance-related behaviors potentially associated with binge drinking [16, 44], collecting information on habits of smoking nicotine cigarettes and/or cannabis during the last 30 days. Furthermore, we checked also for electronic cigarettes (e-cigarettes), a growing phenomenon among young adults [45, 46]. Moreover, we investigated the potential influences of peers on the risk of binge drinking, which may represent important factors associated with binge drinking [28], asking if most of close friends were alcohol drinkers or abstainers. Then, we collected information on the age of onset of alcohol drinking, considering an early onset if it happened before 17 years. Finally, we explored if the subject had high alcohol expectancies for social facilitation [39] through the Alcohol Expectancies Questionnaire for Adolescents, Brief (AEQ-AB) [47]. The AEQ-AB is a seven-item Likert scale exploring alcohol expectancies on global positive changes, changes in social behavior, improved cognitive and motor abilities, sexual enhancement, cognitive and motor impairment, increased arousal, and relaxation and tension reduction [47].

2.5. Statistical Analysis. Statistical analyses were performed using Stata version 10.0 SE. We carried out univariate analyses to identify attributes characteristic of people who binge drink. The normality of continuous data was checked with Shapiro-Wilk's test. Student's t-test was performed for normally

distributed continuous data. If normality assumption was rejected for dependent variable distribution, we used nonparametric Wilcoxon-Mann-Whitney test. Chi-square and Fisher's exact tests were used for categorical variables. We identified covariates significantly associated ($P < 0.05$) with binge drinking for inclusion in subsequent multivariate analyses. Association with binge drinking was shown as odds ratio (OR) with related 95% confidence intervals (CI) and P value. We carried out logistic regressions, controlling for age and sex (as well as adjusting for clusters related to specific place of recruitment) and for variables that were significantly related to binge drinking in the univariate analyses.

3. Results

3.1. Participants. We recruited 654 potentially eligible subjects, with 590 (90.2%) meeting our inclusion criteria. No eligible individual refused to participate in the study. The sample comprised 286 males (48.5% of sample) and 304 females (51.5%). The mean age (±standard deviation) was 20.65 ± 1.90, with no significant gender differences. Most of selected subjects were born in Italy, lived with parents, were single in their undergraduate higher education, and not yet in formal employment. Sociodemographical characteristics of the sample are fully described in Table 1.

For most of the variables, we had no missing data, although for possibly sensitive items of questionnaires response rates ranged from 96.3% (*being in a relationship*) to 99.5% (*religiosity*; *living alone or with parents*; *anxiety*; *depression*; *financial availability for each weekend*).

Table 1: Sociodemographic characteristics.

Variable	Cases (n)	Prevalence (%)
Gender		
Male	286	48.5
Female	304	51.5
Age		
18-19 yrs	178	30.2
20–22 yrs	300	50.8
23-24 yrs	112	19.0
Place of birth		
Italy	547	92.7
Abroad	43	7.3
Living with parents		
Yes	446	75.9
No	142	24.1
In a relationship		
Yes	237	41.7
No	331	58.3
Educational status		
Nonstudent	79	13.4
High school student	162	27.5
University student	349	59.1
Full- or part-time work		
Yes	178	30.7
No	402	69.3

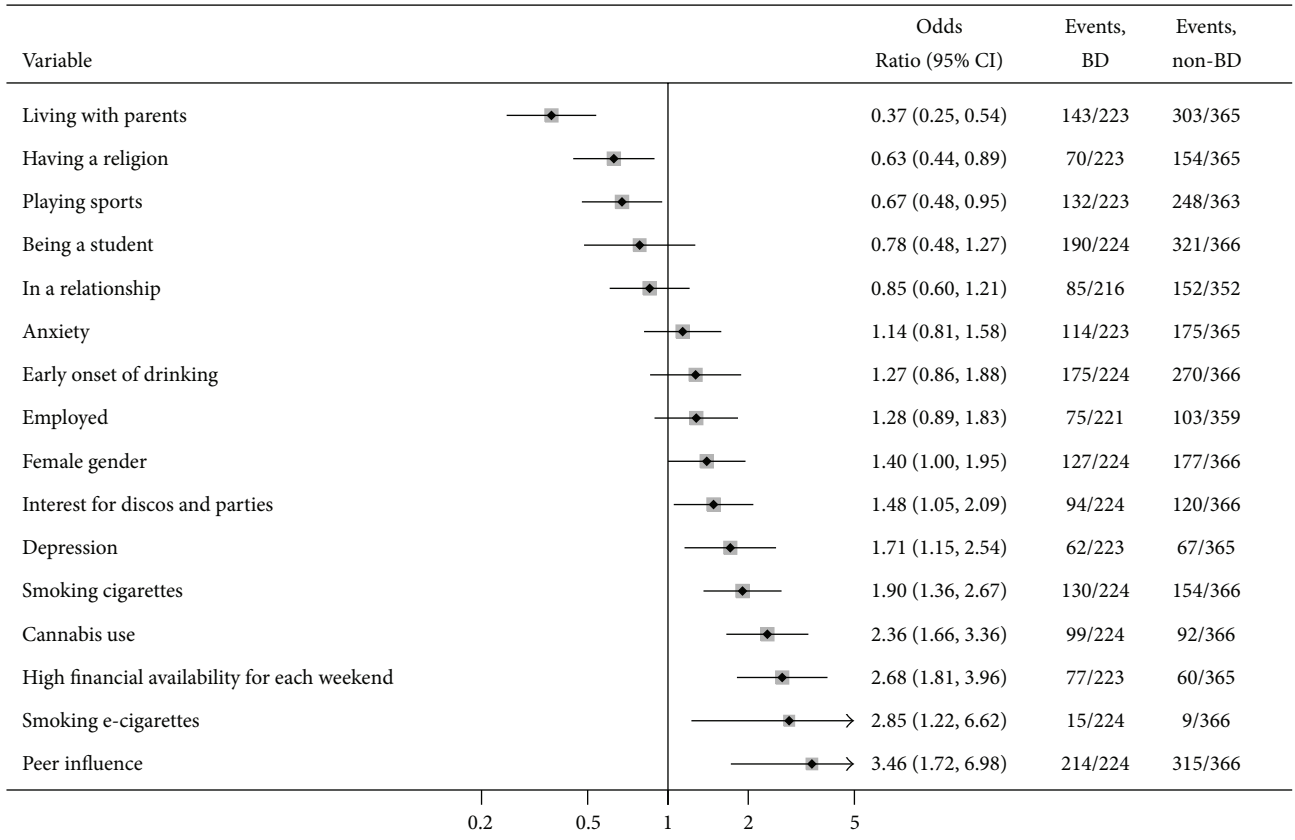
3.2. Univariate Analysis. People with a recent binge drinking were 224 (38.0% of the sample). Rates of a recent binge drinking were significantly higher among females than males (41.8% versus 33.9%; $P = 0.049$). Binge drinkers were significantly older than their nonbinge drinking counterpart (21.1 ± 1.9 versus 20.3 ± 1.9 years; $P < 0.001$). People who recently engaged in binge drinking showed higher scores of both impulsivity ($P < 0.001$) and alcohol expectancies ($P < 0.001$) according to SURPS and AEQ-AB scales, respectively. Furthermore, depressive disorders were more frequent among binge drinkers than in nonbinge drinking individuals (27.8% versus 18.4%; $P = 0.007$), but no statistical differences were found for what concerns anxiety symptoms (51.1% versus 47.9%; $P = 0.455$). All smoking habits appeared significantly related to a recent binge drinking episode: cigarettes, cannabis, and e-cigarettes were regularly used by 58.0%, 44.2%, and 6.7% of binge drinkers, and by 42.1%, 25.1%, and 2.5% of nonbinge drinkers, respectively. Univariate analyses showed that having a high interest for parties and discos ($P = 0.024$), having more than €50 available *per* weekend ($P < 0.001$), and having most of friends drinking alcohol ($P < 0.001$) all were significantly associated with a recent binge drinking episode. On the other hand, young people living with parents ($P < 0.001$), playing sport ($P = 0.025$), or who claimed to be religious ($P = 0.009$) were less likely to have been recently engaged in binge drinking. Univariate analyses for categorical and continuous variables are detailed in Figure 1 and Table 2.

3.3. Multivariate Analysis. We performed multivariate analysis, taking into account age, gender, place of recruitment, and all variables significantly associated with binge drinking at univariate analyses. Results are described in Table 3. Positive alcohol expectancies ($P < 0.001$), a high financial availability for each weekend ($P = 0.041$), interest for parties and discos ($P < 0.006$), female gender ($P < 0.001$), cannabis use ($P = 0.003$), influence by peers ($P < 0.001$), and e-cigarettes smoking ($P = 0.047$) all were significant correlates of binge drinking. On the other hand, living with parents appeared significantly protective ($P = 0.031$). Other variables included in the multivariate analysis, such as age ($P = 0.127$), cigarettes smoking ($P = 0.841$), impulsivity ($P = 0.229$), playing sport ($P = 0.506$), religiosity ($P = 0.333$), depressive symptoms ($P = 0.384$), were not significantly associated with the likelihood of a recent episode of binge drinking.

4. Discussion

4.1. Summary and Interpretation of Findings. This study describes the prevalence and correlates of binge drinking in a large representative sample of Italian alcohol consuming young adults, recruited in the Milan night scene.

Binge drinking prevalence was 38%, significantly higher among females than males, as confirmed by the multivariate



BD = binge drinkers
Non-BD = nonbinge drinkers

Figure 1: Correlates of binge drinking: univariate analysis of categorical variables.

Table 2: Correlates of binge drinking: univariate analysis of continuous variables.

Variable	BD (=224)		Non-BD (=366)		Test	OR (95% CI)	P
	Mean	SD	Mean	SD			
Age	21.15	1.87	20.35	1.86	−5.05[a]	1.25 (1.14–1.36)	<0.001
Alcohol expectancies	22.49	3.73	20.79	3.72	−5.33[b]	1.12 (1.08–1.17)	<0.001
Impulsivity	5.55	2.27	4.87	1.96	−3.87[a]	1.17 (1.08–1.26)	<0.001

BD: binge drinkers and non-BD: nonbinge drinkers.
[a]Student's t-test: t.
[b]Mann-Whitney test: z.

analysis. These rates are slightly higher than those reported by previous studies focused exclusively on Italian university students [21, 22]. Furthermore, surprisingly enough, females appeared more likely to have been engaged in a recent episode of binge drinking than males. This finding is different from results of similar studies, for example, [21, 27], in which being male appeared significantly associated with the risk of both recent and lifetime binge drinking. These differences may be explained not only by several conditions, including our settings, recruitment sources, and sociodemographic characteristics, but also by recent changes in drinking habits among young people. Heavy episodic drinking is becoming quite common also in Southern Europe countries, despite their traditional daily but moderate alcohol consumption [25]. Indeed, recent studies report that young women have begun to show drinking patterns similar to those of their male peers, especially regarding heavy episodic drinking [48, 49]. Furthermore, it should be noted that we included in our study only young alcohol consumers, excluding alcohol abstainers. Therefore, both high prevalence and gender difference of binge drinking in our sample may be influenced by the fact that we have analyzed only a subpopulation of young adults at risk for dangerous alcohol-related behaviors. We could hypothesize that, despite the fact that 18–24-year-old females are more often alcohol abstainers than males, according, for example, to evidence on European alcohol

Table 3: Correlates of binge drinking: multivariate analysis*.

Variable	OR (95% CI)	Robust Std. Err.	P
Age	1.19 (0.95–1.48)	0.133	0.127
Female gender	1.57 (1.41–1.75)	0.087	<0.001
Living with parents	0.57 (0.34–0.95)	0.149	0.031
High financial availability for each weekend	1.33 (1.01–1.74)	0.183	0.041
Depression	1.29 (0.73–2.28)	0.375	0.384
Cannabis use	1.61 (1.18–2.20)	0.256	0.003
Smoking cigarettes	1.04 (0.74–1.46)	0.181	0.841
Smoking e-cigarettes	2.49 (1.01–6.18)	1.154	0.047
Impulsivity	1.08 (0.95–1.22)	0.066	0.229
Positive alcohol expectancies	1.11 (1.09–1.13)	0.009	<0.001
Peer influence	2.40 (1.71–3.37)	0.417	<0.001
Interest for discos and parties	1.53 (1.13–2.06)	0.233	0.006
Playing sports	0.93 (0.75–1.15)	0.103	0.506
Having a religion	0.77 (0.45–1.31)	0.209	0.333

* Adjusted for age, gender, and specific place of recruitment.

consumption patterns [50], consuming-alcohol females have a greater risk of being engaged in binge drinking, at least in our geographical area and settings. However, larger studies should be performed to confirm this quite striking result. Our findings show also that binge drinking is significantly related to financial availability, high expectancies from alcohol, use of cannabis, peer influence on drinking patterns, and interest for discos and parties, as similarly reported in other publications of the last 20 years [6, 27, 29, 51–53]. Moreover, this is one of the first studies analyzing the prevalence of the emerging phenomenon of e-cigarettes use [54] in a sample of young adults [45, 46] and its relationship with alcohol risk behaviors. Our study highlighted that smoking electronic cigarettes is significantly associated with a recent episode of binge drinking. However, this finding should be interpreted with caution, since the prevalence of e-cigarettes users in the whole sample was low, corresponding to 6.7% and 2.5% among binge and nonbinge drinkers, respectively. Further studies could be useful to understand if e-cigarettes could be a marker for proneness or vulnerability to sensation seeking and substance consumption, including alcohol and nicotine, given their widespread use among young nonsmokers [55], which is often not part of a smoking quit plan [56]. Living with parents was the only significant protective factor, confirming results from other studies reporting that living outside parental home and far from parental control is associated with a higher risk of binge drinking [57]. None of remaining variables, depressive and anxiety symptoms, cigarettes smoking, impulsive traits of personality, playing sport, and being religious, was statistically associated with recent binge drinking.

4.2. Strengths and Limitations. The main strength of this study is based on representative sampling procedures in natural settings of nightlife scene. Furthermore, any effort to enhance young people participation has been implemented, including peer interviewers, use of smartphone, and financial incentive. This may explain the high response rates. However, also several limitations need to be acknowledged, first the cross-sectional design, which prevents from identifying causal links between binge drinking and related factors. Moreover, in the quick, 10-minute-questionnaire, a number of sensitive correlates (e.g., average amount of alcohol use, exposure to previous traumatic events, family habits with drinking, and consumption of drugs other than nicotine and cannabis) had to be excluded, though the literature has shown relevant correlations with binge drinking [6, 58, 59]. For the same reason, we did not use standardized interviews to detect mental disorders, and the anxiety and depression symptoms were checked only with a single item question, though psychometric properties of this approach are quite satisfactory [35]. Finally, since our survey was based on a single urban area of Northern Italy, the results of our study may not be generalizable to the whole Italian general population of young adults.

4.3. Conclusions. More than a third of young adults using alcohol from our sample were recent binge drinkers. This is slightly higher than rates of other studies from similar geographical areas [21, 22], representing a potential serious risk to public health, because of high risk of adverse consequences [14]. There is the need of developing specific interventions for primary and secondary prevention, and public health research should focus on new programs that may reduce rates of binge drinking or, at least, its adverse health outcomes [27, 60]. At the same time, prevention strategies should be linked with changes of general public attitudes often considering binge drinking as an acceptable "rite of passage" of adolescents and young adults, with fewer dangerous health consequences than other illicit substance-related risky behaviors [3].

Conflict of Interests

The authors have no conflict of interests regarding the publication of this paper.

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References

[1] M. Tomsovic, "'Binge' and continuous drinkers. Characteristics and treatment follow up," *Quarterly Journal of Studies on Alcohol*, vol. 35, no. 2, part A, pp. 558–564, 1974.

[2] H. Wechsler, G. W. Dowdall, A. Davenport, and E. B. Rimm, "A gender-specific measure of binge drinking among college students," *The American Journal of Public Health*, vol. 85, no. 7, pp. 982–985, 1995.

[3] T. S. Naimi, R. D. Brewer, A. Mokdad, C. Denny, M. K. Serdula, and J. S. Marks, "Binge drinking among US adults," *Journal of the American Medical Association*, vol. 289, no. 1, pp. 70–75, 2003.

[4] M. A. Plant, M. L. Plant, P. Miller, G. Gmel, and S. Kuntsche, "The social consequences of binge drinking: a comparison of young adults in six european countries," *Journal of Addictive Diseases*, vol. 28, no. 4, pp. 294–308, 2009.

[5] W. S. Slutske, "Alcohol use disorders among US college students and their non-college-attending peers," *Archives of General Psychiatry*, vol. 62, no. 3, pp. 321–327, 2005.

[6] E. Kuntsche, J. Rehm, and G. Gmel, "Characteristics of binge drinkers in Europe," *Social Science and Medicine*, vol. 59, no. 1, pp. 113–127, 2004.

[7] W. Farke and P. Anderson, "Binge drinking in Europe," *Adicciones*, vol. 19, no. 4, pp. 333–339, 2007.

[8] R. Hanewinkel, J. D. Sargent, E. A. P. Poelen et al., "Alcohol consumption in movies and adolescent binge drinking in 6 European countries," *Pediatrics*, vol. 129, no. 4, pp. 709–720, 2012.

[9] E. Webb, C. H. Ashton, P. Kelly, and F. Kamali, "Alcohol and drug use in UK university students," *The Lancet*, vol. 348, no. 9032, pp. 922–925, 1996.

[10] G. Martinotti, V. Carli, D. Tedeschi et al., "Mono- and polysubstance dependent subjects differ on social factors, childhood trauma, personality, suicidal behaviour, and comorbid Axis I diagnoses," *Addictive Behaviors*, vol. 34, no. 9, pp. 790–793, 2009.

[11] M. Driessen, C. Veltrup, J. Weber, U. John, T. Wetterling, and H. Dilling, "Psychiatric co-morbidity, suicidal behaviour and suicidal ideation in alcoholics seeking treatment," *Addiction*, vol. 93, no. 6, pp. 889–894, 1998.

[12] R. M. Viner and B. Taylor, "Adult outcomes of binge drinking in adolescence: findings from a UK national birth cohort," *Journal of Epidemiology and Community Health*, vol. 61, no. 10, pp. 902–907, 2007.

[13] Y. A. Bonomo, G. Bowes, C. Coffey, J. B. Carlin, and G. C. Patton, "Teenage drinking and the onset of alcohol dependence: A cohort study over seven years," *Addiction*, vol. 99, no. 12, pp. 1520–1528, 2004.

[14] J. W. Miller, T. S. Naimi, R. D. Brewer, and S. E. Jones, "Binge drinking and associated health risk behaviors among high school students," *Pediatrics*, vol. 119, no. 1, pp. 76–85, 2007.

[15] S. E. Jones, J. Oeltmann, T. W. Wilson, N. D. Brener, and C. V. Hill, "Binge drinking among undergraduate college students in the United States: implications for other substance use," *The Journal of American College Health*, vol. 50, no. 1, pp. 33–38, 2001.

[16] R. Siliquini, A. Colombo, P. Berchialla, and F. Bert, "Binge drinking and psychoactive drug use in a cohort of European youths," *Journal of Public Health Research*, vol. 1, article e15, 2012.

[17] G. Martinotti, G. di Iorio, D. Tedeschi et al., "Prevalence and intensity of basic symptoms among cannabis users: an observational study," *The American Journal of Drug and Alcohol Abuse*, vol. 37, no. 2, pp. 111–116, 2011.

[18] B. C. Haberstick, S. E. Young, J. S. Zeiger, J. M. Lessem, J. K. Hewitt, and C. J. Hopfer, "Prevalence and correlates of alcohol and cannabis use disorders in the United States: results from the national longitudinal study of adolescent health," *Drug and Alcohol Dependence*, vol. 136, pp. 158–161, 2014.

[19] M. E. Patrick, J. E. Schulenberg, M. E. Martz, J. L. Maggs, P. M. O'Malley, and L. D. Johnston, "Extreme binge drinking among 12th-grade students in the United States: prevalence and predictors," *JAMA Pediatrics*, vol. 167, no. 11, pp. 1019–1025, 2013.

[20] G. Carrà, S. Johnson, P. Bebbington et al., "The lifetime and past-year prevalence of dual diagnosis in people with schizophrenia across Europe: Findings from the European Schizophrenia Cohort (EuroSC)," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 262, no. 7, pp. 607–616, 2012.

[21] L. DiGrande, M. P. Perrier, M. G. Lauro, and P. Contu, "Alcohol use and correlates of binge drinking among university students on the island of Sardinia, Italy," *Substance Use and Misuse*, vol. 35, no. 10, pp. 1471–1483, 2000.

[22] M. D'Alessio, R. Baiocco, and F. Laghi, "The problem of binge drinking among Italian university students: a preliminary investigation," *Addictive Behaviors*, vol. 31, no. 12, pp. 2328–2333, 2006.

[23] F. Laghi, R. Baiocco, A. Lonigro, G. Capacchione, and E. Baumgartner, "Family functioning and binge drinking among Italian adolescents," *Journal of Health Psychology*, vol. 17, no. 8, pp. 1132–1141, 2012.

[24] H. Soler-Vila, I. Galán, J. L. Valencia-Martín, L. M. León-Muñoz, P. Guallar-Castillón, and F. Rodríguez-Artalejo, "Binge Drinking in Spain, 2008–2010," *Alcoholism: Clinical and Experimental Research*, vol. 38, no. 3, pp. 810–819, 2014.

[25] P. Mäkelä, G. Gmel, U. Grittner et al., "Drinking patterns and their gender differences in Europe," *Alcohol and Alcoholism*, vol. 41, no. 1, pp. i8–i18, 2006.

[26] E. von Elm, M. Egger, STROBE Initiative et al., "Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies," *British Medical Journal*, vol. 335, no. 7624, pp. 806–808, 2007.

[27] H. Wechsler, G. W. Dowdall, A. Davenport, and S. Castillo, "Correlates of college student binge drinking," *The American Journal of Public Health*, vol. 85, no. 7, pp. 921–926, 1995.

[28] E. R. Weitzman, T. F. Nelson, and H. Wechsler, "Taking up binge drinking in college: the influences of person, social group, and environment," *Journal of Adolescent Health*, vol. 32, no. 1, pp. 26–35, 2003.

[29] K. E. Courtney and J. Polich, "Binge drinking in young adults: data, definitions, and determinants," *Psychological Bulletin*, vol. 135, no. 1, pp. 142–156, 2009.

[30] Z. M. Sanchez, S. S. Martins, E. S. Opaleye, Y. G. Moura, D. P. Locatelli, and A. R. Noto, "Social factors associated to binge drinking: a cross-sectional survey among Brazilian students in private high schools," *BMC Public Health*, vol. 11, article 201, 2011.

[31] G. Carrà and S. Johnson, "Variations in rates of comorbid substance use in psychosis between mental health settings and geographical areas in the UK," *Social Psychiatry and Psychiatric Epidemiology*, vol. 44, no. 6, pp. 429–447, 2009.

[32] G. Carrà, R. Scioli, M. C. Monti, and A. Marinoni, "Severity profiles of substance-abusing patients in Italian community addiction facilities: Influence of psychiatric concurrent disorders," *European Addiction Research*, vol. 12, no. 2, pp. 96–101, 2006.

[33] G. Carrà, F. Bartoli, C. Crocamo, K. T. Brady, and M. Clerici, "Attempted suicide in people with co-occurring bipolar and substance use disorders: systematic review and meta-analysis," *Journal of Affective Disorders*, vol. 167, pp. 125–135.

[34] T. Paljärvi, M. Koskenvuo, K. Poikolainen, J. Kauhanen, L. Sillanmäki, and P. Mäkelä, "inge drinking and depressive symptoms: a 5-year population-based cohort study," *Addiction*, vol. 104, no. 7, pp. 1168–1178, 2009.

[35] A. J. Mitchell and J. C. Coyne, "Do ultra-short screening instruments accurately detect depression in primary care? A pooled analysis and meta-analysis of 22 studies," *The British Journal of General Practice*, vol. 57, no. 535, pp. 144–151, 2007.

[36] G. Carrà, P. Sciarini, G. Segagni-Lusignani, M. Clerici, C. Montomoli, and R. C. Kessler, "Do they actually work across borders? Evaluation of two measures of psychological distress as screening instruments in a non Anglo-Saxon country," *European Psychiatry*, vol. 26, no. 2, pp. 122–127, 2011.

[37] S. C. C. M. Teunissen, A. de Graeff, E. E. Voest, and J. C. J. M. de Haes, "Are anxiety and depressed mood related to physical symptom burden? A study in hospitalized advanced cancer patients," *Palliative Medicine*, vol. 21, no. 4, pp. 341–346, 2007.

[38] I. M. Balodis, M. N. Potenza, and M. C. Olmstead, "Binge drinking in undergraduates: relationships with sex, drinking behaviors, impulsivity, and the perceived effects of alcohol," *Behavioural Pharmacology*, vol. 20, no. 5-6, pp. 518–526, 2009.

[39] J. M. Townshend, N. Kambouropoulos, A. Griffin, F. J. Hunt, and R. M. Milani, "Binge drinking, reflection impulsivity, and unplanned sexual behavior: impaired decision-making in young social drinkers," *Alcoholism: Clinical and Experimental Research*, vol. 38, no. 4, pp. 1143–1150, 2014.

[40] P. A. Woicik, S. H. Stewart, R. O. Pihl, and P. J. Conrod, "The substance use risk profile scale: a scale measuring traits linked to reinforcement-specific substance use profiles," *Addictive Behaviors*, vol. 34, no. 12, pp. 1042–1055, 2009.

[41] L. Gallimberti, S. Chindamo, A. Buja et al., "Underage drinking on saturday nights, sociodemographic and environmental risk factors: a cross-sectional study," *Substance Abuse: Treatment, Prevention, and Policy*, vol. 6, no. 1, article 15, 2011.

[42] A. L. Sønderlund, K. O'Brien, P. Kremer et al., "The association between sports participation, alcohol use and aggression and violence: a systematic review," *Journal of Science and Medicine in Sport*, vol. 7, no. 1, pp. 2–7, 2014.

[43] J. M. Mellor and B. A. Freeborn, "Religious participation and risky health behaviors among adolescents," *Health Economics*, vol. 20, no. 10, pp. 1226–1240, 2011.

[44] M. B. Reed, R. Wang, A. M. Shillington, J. D. Clapp, and J. E. Lange, "The relationship between alcohol use and cigarette smoking in a sample of undergraduate college students," *Addictive Behaviors*, vol. 32, no. 3, pp. 449–464, 2007.

[45] E. L. Sutfin, T. P. McCoy, H. E. R. Morrell, B. B. Hoeppner, and M. Wolfson, "Electronic cigarette use by college students," *Drug and Alcohol Dependence*, vol. 131, no. 3, pp. 214–221, 2013.

[46] K. Choi and J. L. Forster, "Beliefs and experimentation with electronic cigarettes: a prospective analysis among young adults," *The American Journal of Preventive Medicine*, vol. 46, no. 2, pp. 175–178, 2014.

[47] L. A. R. Stein, B. Katz, S. M. Colby et al., "Validity and reliability of the alcohol expectancy questionnaire-adolescent, brief," *Journal of Child and Adolescent Substance Abuse*, vol. 16, no. 2, pp. 115–127, 2007.

[48] A. M. Young, M. Morales, S. E. McCabe, C. J. Boyd, and H. D'Arcy, "Drinking like a guy: frequent binge drinking among undergraduate women," *Substance Use and Misuse*, vol. 40, no. 2, pp. 241–267, 2005.

[49] C. Andersson, V. Sundh, M. Waern, A. Jakobsson, L. Lissner, and F. Spak, "Drinking context and problematic alcohol consumption in young Swedish women," *Addiction Research & Theory*, vol. 21, no. 6, pp. 457–468, 2013.

[50] World Health Organization, *European Information System on Alcohol and Health (EISAH). Patterns of Consumption: Abstainers (18–24 years), Lifetime by Country*, World Health Organization, Geneva, Switzerland, 2014.

[51] T. P. S. Oei and A. Morawska, "A cognitive model of binge drinking: the influence of alcohol expectancies and drinking refusal self-efficacy," *Addictive Behaviors*, vol. 29, no. 1, pp. 159–179, 2004.

[52] C. J. Boyd, S. E. McCabe, and M. Morales, "College students' alcohol use: a critical review," *Annual Review of Nursing Research*, vol. 23, pp. 179–211, 2005.

[53] J. A. Cranford, S. E. McCabe, and C. J. Boyd, "A new measure of binge drinking: prevalence and correlates in a probability sample of undergraduates," *Alcoholism: Clinical and Experimental Research*, vol. 30, no. 11, pp. 1896–1905, 2006.

[54] P. Caponnetto, D. Campagna, G. Papale, C. Russo, and R. Polosa, "The emerging phenomenon of electronic cigarettes," *Expert Review of Respiratory Medicine*, vol. 6, no. 1, pp. 63–74, 2012.

[55] J. S. Brody, "The promise and problems of e-cigarettes," *American Journal of Respiratory and Critical Care Medicine*, vol. 189, no. 4, pp. 379–380, 2014.

[56] D. L. Palazzolo, "Electronic cigarettes and vaping: a new challenge in clinical medicine and public health. A literature review," *Front Public Health*, vol. 1, article 56, 2013.

[57] E. R. Weitzman, Y. Chen, and S. V. Subramanian, "Youth smoking risk and community patterns of alcohol availability and control: a national multilevel study," *Journal of Epidemiology and Community Health*, vol. 59, no. 12, pp. 1065–1071, 2005.

[58] D. Deas, "Adolescent substance abuse and psychiatric comorbidities," *Journal of Clinical Psychiatry*, vol. 67, supplement 7, pp. 18–23, 2006.

[59] L. Strunin, K. Lindeman, E. Tempesta, P. Ascani, S. Anav, and L. Parisi, "Familial drinking in Italy: harmful or protective factors," *Addiction Research and Theory*, vol. 18, no. 3, pp. 344–358, 2010.

[60] F. Bartoli, G. Carrà, G. Brambilla et al., "Association between depression and non-fatal overdoses among drug users: a systematic review and meta-analysis," *Drug and Alcohol Dependence*, vol. 134, pp. 12–21, 2014.

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Review Article

Sexual Enhancement Products for Sale Online: Raising Awareness of the Psychoactive Effects of Yohimbine, Maca, Horny Goat Weed, and *Ginkgo biloba*

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Introduction. The use of unlicensed food and herbal supplements to enhance sexual functions is drastically increasing. This phenomenon, combined with the availability of these products over the Internet, represents a challenge from a clinical and a public health perspective. *Methods*. A comprehensive multilingual assessment of websites, drug fora, and other online resources was carried out between February and July 2013 with exploratory qualitative searches including 203 websites. Additional searches were conducted using the Global Public Health Intelligence Network (GPHIN). Once the active constitutes of the products were identified, a comprehensive literature search was carried out using PsycInfo and PubMed. *Results*. The most common sexual enhancement products available on the Internet were identified. Their active ingredients included yohimbine, maca, horny goat weed and *Ginkgo biloba*. These four substances were reported with the occurrence of adverse events and the induction of psychological symptoms, such as mood changes, anxiety, and hallucinations as well as addictive behaviours. *Conclusions*. Uncontrolled availability of sexual enhancement products that contain potentially harmful substances is a major public health concern. The possible impact on population health, particularly among subjects with psychiatric disorders, usually at risk for sexual dysfunction, may be significant. This new trend needs to be extensively studied and monitored.

1. Introduction

The use of food and herbal supplements to enhance erectile function as well as sexual arousal and desire has become increasingly popular in the recent years [1, 2]. These products are advertised on the Internet as "*natural*" and "*safer*" alternatives to pharmaceutical products, such as gold standard for treatment of erectile dysfunction and the phosphodiesterase type 5 (PDE5) inhibitors (e.g., sildenafil, tadalafil, and vardenafil). However, they often contain potent active constituents [3–5], which remain undeclared on the packaging [6, 7]. The effects of the aforementioned products, thus, remain unknown until reports on harms expose the problem and accurate clinical evaluation takes place.

Since herbal supplements are plant products, they are generally perceived and hence marketed as natural and, therefore, "safe" [8]. However, several case reports of side effects to herbs and herbal products have been reported [8, 9], such as on- and off-target effects from biologically active ingredients, side effects caused by contaminants, and herb-drug interactions. It is difficult to determine the true frequency of side effects from herbs and herbal products, since surveillance systems are much less extensive than those in place for pharmaceutical drugs. It is estimated that less than 1% of side effects or adverse events for herbal products are recorded with the current surveillance systems [10].

Some of the side effects and adverse events due to ingestion of herbs and herbal products are related to their

action on central nervous system and can present as mood alterations, anxiety, mania, depression, hallucinations, and addictive behaviour; one example of such herbal product is ephedra, which was banned in the USA in 2004 [11].

However, psychological safety profiles of sexual enhancement products have not been characterised. This review, therefore, aimed at identifying the sexual enhancement products advertised and sold on the Internet while collecting information about their characteristics (i.e., brand names, costs, ingredients, availability, declared advantages, and disadvantages). We then focused on four substances, which are common in these products: yohimbine, maca, horny goat weed, and *Ginkgo biloba*, as these were reported to induce psychological side effects. We also described, less in detail, other components of sexual enhancer products that may have both somatic and psychological side effects.

2. Methods

A multilingual qualitative assessment of a range of websites, drug fora, and other online resources (i.e., e-commerce, e-newsgroups, chat rooms, videos, e-newsletters, and bulletin boards) was carried out between February 2012 and May 2013. Exploratory qualitative searches of 203 websites in English and Italian took place using brand names through Google search engine. Of these, 106 were considered to be relevant for the study and as such were monitored on a regular basis, that is daily ($n = 21$), weekly ($n = 32$), or monthly ($n = 53$), depending on their relevance. The remaining 97 websites were considered not to bear any interest for the present study and thus were no longer monitored. Further specific searches in the database provided by The Global Public Health Intelligence Network (GPHIN) also took place. This is a secure Internet-based early warning system that gathers preliminary reports of public health significance by monitoring global media sources near "real-time," 24 hours a day, 7 days a week basis. GPHIN is operated by the Public Health Agency of Canada and monitors news sources and websites across the globe in 9 languages (e.g., English, French, Farsi, Portuguese, Arabic, Russian, Spanish, and Chinese simplified/traditional) [12]. While a series of algorithms were used and adjusted to capture relevant information, analysis of relevant data since 2003 was also carried out manually by a multidisciplinary and multilingual team of analysts. Finally, once the active constituents of these products were identified, a comprehensive literature search was carried out using PsycInfo and Pubmed databases. Permission for the study was granted by the School of Pharmacy Ethics Committee, Hatfield, UK (15 December, 2010; PHAEC/10-42).

3. Results

During the website assessment stage where 136 websites were monitored for 6 months, we have identified 15 sexual enhancement products advertised and sold on the Internet. The characteristics of these products are summarized in Table 1. Yohimbe, ginseng, *Ginkgo biloba*, maca, horny goat weed, and L-arginine were claimed to be the most common ingredients in those products. Among all the substances identified in these products, we have found psychological safety concerns for only four: yohimbine, maca, horny goat weed, and *Ginkgo biloba*. Biological, pharmacological, and safety profiles of these four substances are presented below.

3.1. Yohimbine

3.1.1. Source and Preparations. Yohimbine is a natural tryptamine alkaloid, which can be extracted from the bark of a variety of plants mostly of African and Asian origin such as *Pausinystalia yohimbe* (also known as yohimbe tree) and the root of *Rauvolfia serpentina*. Yohimbe bark extract is traditionally used in Africa as an aphrodisiac: it has to be underlined, though, that tree bark does contain a large number of alkaloids, and yohimbine level in this natural source may be low. Yohimbine concentration has been suggested to increase in older branches [13]. A 1995 study by Betz et al. on dietary supplements containing Yohimbe extracts has shown that the yohimbine content may range from < 0.1 to 489 ppm compared with 7089 ppm in the authentic material, which has been attributed to the intense dilution of final product [14]. Currently, yohimbine-containing products are advertised on the Internet not only for treating erectile dysfunction and enhancing sexual performance, but also as a fast weight-loss and body-building supplement [15–17]. Brand names include "The Millennium Male Horse Power Capsule" [18], Syntrax [15], and Xytomax (see Table 1).

3.1.2. Mechanism of Action. Yohimbine has high affinity to human alpha-2 adrenoceptors, moderate affinity to alpha-1 adrenoceptors, and low affinity to some of the serotonin and dopamine receptors in the central and peripheral nervous systems [19]. Alpha-2 adrenoceptors mediate erection-inhibiting impulses in the central nervous system. Yohimbine is generally believed to enhance central sexual impulse by blocking the alpha-2 adrenoceptors in the locus coeruleus in the brain [20]. In the periphery, yohimbine has been suggested to inhibit alpha-1 and alpha-2 adrenoceptors as well as enhancing the release of nitric oxide (NO) from cavernosal endothelial cells [21, 22]. In conclusion, the mechanism of action of yohimbine in enhancing sexual function is currently unclear.

3.1.3. Pharmacokinetics. Yohimbine hydrochloride is rapidly absorbed and the maximum plasma concentration is generally achieved in less than one hour after oral administration [23, 24]. The mean bioavailability is low and is subject to very high variation from one individual to another [25]. The plasma concentration of yohimbine does not appear to correlate with the dose of the compound administered [26].

3.1.4. Efficacy. A meta-analysis in 1998 of seven clinical trials with yohimbine has shown a superiority of the compound over placebo in treatment of erectile dysfunction [27]. Yohimbine has also been reported to be effective in treatment of orgasmic disorders such as delayed ejaculation [28]. There have been no clinical studies testing Yohimbe bark. The Clinical Guidelines Panel on Erectile Dysfunction of the American

Table 1: Characteristics of sexual enhancer products sold online.

Brand name	Ingredients	Cost	Availability	Effects/declared advantages from anecdotal online reports	Side effects/disadvantages from anecdotal online reports
Endowmax http://www.endowmax.com/	*Epimedium grandiflorum* (horny goat weed); maca; damiana; L-arginine; *Tribulus terrestris*; gamma-aminobutyric acid; jujube dates extracts; Muira puama (potency woods); Catuaba bark; *Xanthoparmelia scabrosa*; *Cnidium monnieri*; Tongkat Ali (*Eurycoma longifolia*)	59.95 $ per box; six-month supply for 239.95 $	Online suppliers (orders can be placed by fax and phone); Ebay; Amazon (currently out of stock).	Powerful and natural; no unpleasant side effects; customers testimonials; money back guarantee; it is clearly stated the product does not contain Yohimbe.	Up to 8 weeks for initial benefits; expensive.
Xytomax http://www.xytomax.com/	Niacinamide (vitamin B3); zinc oxide; *Epimedium sagittatum* (standardized to 10% icariin); maca root; Guarana extract (standardized to 20% caffeine); Korean ginseng root; L-arginine; Muira puama; Longjack extract; *Avena sativa*; Yohimbe bark extract (2% yohimbine); *Ginkgo biloba* extract (24% flavonglycodises & 6% terpene lactones); saw palmetto (berry); *Xanthoparmelia Scabrosa*; *Cnidium monnieri* extract; GABA; damiana (leaf)	69.96 $ per box; six-month supply for 309.95 $	Online suppliers (orders can be placed by fax and phone); Ebay.	Natural; working from the very first dose; customers testimonials; money back guarantee.	It is not to be used in case of thyroid, kidney, or heart diseases or high blood pressure; more expensive than other products.
Xanogen http://www.xanogen.com/	*Epimedium grandiflorum* (horny goat weed); maca; Yohimbe; L-arginine; *Tribulus terrestris*; gamma-aminobutyric acid; Muira puama (potency woods); Catuaba bark; *Xanthoparmelia scabrosa*; *Cnidium Monnieri*	89.95 $ per box; six-month supply for 419.95 $	Online suppliers (orders can be placed by fax and phone); Ebay; Amazon (currently out of stock).	100% natural products; money back guarantee; no negative side effects; permanent effects on corpora cavernosa.	It could cause stomach upset if not taken with food; it does not provide immediate erections but stronger ones.
Virility EX http://www.virilityex.it/	Yohimbe; maca; Elk Antler Velvet; Eleuthero; Longjack; Muira puama (potency woods); Catuaba bark; oat straws.	29.89 € per box; six-month supply for 89.74 €	Online suppliers (orders can be placed by fax and phone); Ebay; Amazon (currently unavailable).	Stated as: "No side effects; 100% natural; money back guarantee."	Some users claim no results with this product; just a couple of customer testimonials were found on official websites with no FAQ sections.
Enzyte http://www.enzyte.com/	Korean red ginseng; *Gingko biloba*; grape seed extract; horny goat weed; Muira puama; niacin; zinc.	39.95 $ per box; six-month supply for 179 $	Online suppliers; Ebay; Amazon.	Premium natural ingredients; no gluten, no preservatives, no ephedra, no caffeine, no Yohimbe.	Reported hives, facial flushing, insomnia, and internal bleeding; some users claim no results with this product.

Table 1: Continued.

Brand name	Ingredients	Cost	Availability	Effects/declared advantages from anecdotal online reports	Side effects/disadvantages from anecdotal online reports
Extagen http://www.extagen.com/	Not clearly listed on website, just "herbs and phytonutrients."	59 $ per box; six-month supply for 198 $; twelve-month supply for 288 $	Online suppliers (orders can be placed by phone, and mail too); Ebay; Amazon.	Natural, vegetarian and hypoallergenic; money back guarantee; it is clearly stated the product does not contain Yohimbe; customers testimonials.	Contraindicated in case of high blood pressure or other medical conditions.
Extenze http://www.extenze.net	L-Arginine; Eleutherococcus; Yohimbe bark extract; nettle; ginseng; folate; micronized DHEA; Muira puama; pregnenolone; zinc; black pepper; *Piper longum*; ginger. *Cnidium monnieri*; *Astragalus*: *Xanthoparmelia Scabrosa*; boron; GABA; velvet deer antler; horny goat weed; damiana; pumpkin; licorice extract; Ho Shou Wu extract.	59.95 $ per box; six-month supply for 305.95 $; ten-month supply for 499.95 $	Online suppliers (orders can be placed by fax, phone, and mail too); Ebay.	Stated as: "all natural; assures penis enlargement in addition to increasing sexual stamina; customers testimonials; money back guarantee."	Legal controversies; reported increased heart rates, agitation, and nervousness.
Maxidus http://www.maxidus-pill.com/	*Eurycoma longifolia*; *Flos catharmi*; Rizoma *Curcumae longae*; *Gingko biloba*; Herba Epimedii; Herba Cistanches; *Astragalus membranaceus*; *Momordica charantia* L (Ku Gua).	39.95 $ per box; six-month supply for 399.75 $; twelve-month supply for 479.40 $	Online suppliers (orders can be placed by fax, phone, and mail too); Ebay.	Stated as: "works in 10–30 minutes and lasts for up to 4 days; money back guarantee; 100% natural; it can be taken by people with heart or prostate problems, hypertension, diabetes; it can be used by women too."	Slight headache reported; expensive; clinical tests carried out are shown for only one ingredient (*Eurycoma longifolia*).
Orexis http://www.orexis-pills.co.uk	*Tribulus terrestris*; Epimedium sagittatum; Muira puama; *Panax ginseng*; Catuaba bark extract; damiana; Yohimbe extract.	29.16 £ per box; six-month supply for 135.00 £; twelve-month supply for 262.50 £	Online suppliers (orders can be placed by fax, phone, and mail too); Ebay.	Stated as: "all natural; works within 45 minutes; customers testimonials; money back guarantee."	Legal issues; interaction with antidepressants, diuretics, and high blood pressure medications.
Pro Solution Pills http://www.prosolu-tionpills.com/	Solidilin; Korean ginseng; Butea superba; *Momordica*; apigenin; Amla; Arjuna; *Cordyceps*; zinc oxide: reishi mushroom; *Curculigo*; drilizen; bladderwrack.	59.95 $ per box; six-month supply for 289.95 $; twelve-month supply for 399.95 $	Online suppliers (orders can be placed by fax, phone, and mail); Ebay; Amazon.	Stated as "all natural; no side effects; multiple orgasms per sexual encounter; customers testimonials; money back guarantee."	Reported nausea, hypertension; increased heart rate, dizziness; it needs 5-6 months before the user notices the desired results.

Table 1: Continued.

Brand name	Ingredients	Cost	Availability	Effects/declared advantages from anecdotal online reports	Side effects/disadvantages from anecdotal online reports
Provigro http://www.provigro.com	Horny goat weed; maca root; saw palmetto; Tongkat Ali; *Mucuna pruriens* 10% L-dopa; Muira puama; L-arginine; *Panax ginseng*.	34.97 $ per box; three-month supply for 57.80 $	Online suppliers (orders can be placed by fax, phone, and mail).	Stated as "natural vitamins, minerals and herbs"; customers testimonials; money back guarantee; it does not contain Yohimbe.	Reported nausea, dizziness, and vomiting; it may take up to six months to work.
Quantum Pills http://www.quantumpills.com	L-arginine; L-lysine HCL; maca root; Muira puama; Swedish flower pollen extract; horny goat weed; Catuaba bark; *Gingko biloba*; zinc oxide.	44.95 $ per box; six-month supply for 189.95 $	Online suppliers (orders can be placed by fax, phone, and mail too).	Stated as a "climax enhancer," assures increase in ejaculation volume; natural; money back guarantee; customers testimonials.	No permanent results; no scientific proofs and no adequate ingredients explanation.
Sinrex http://www.sinrex.com	Bioperine; copper chelate; creatine; Cuscuta seed; *Gingko biloba*; green tea extract; Hawthorn berries; Epunedum Sagitum; inosine; L-arginine; maca; omega 3; saw palmetto; Siberian ginseng; soy proteins; *Tribulus terrestris*; vitamin E.	39.95 $ per box; six-month supply for 199.95 $	Online suppliers (orders can be placed by fax, phone, and mail too); Ebay.	Presented as "all natural; money back guarantee; customers testimonials; semen volume and orgasm intensifier."	At least one month for initial results; possible allergies to ingredients.
Sizepro http://www.sizepro.com	Vitamin E; vitamin B3; horny goat weed; hawthorn berry; damiana; Muira puama; *Gingko biloba*; Chinese ginseng; *Tribulus* fruit extract; Catuaba bark; saw palmetto; inosine; L-arginine; oat straw; cayenne fruit; soy protein.	Two-month supply for 99.95 $; six-month supply for 245.95 $	Online suppliers (orders can be placed by fax, phone, and mail too); Ebay.	Natural; "Lasting increase of penis thickness and size; money back guarantee; customers testimonials."	
Vazomyne http://www.vazomyne.net	Not completely listed. Vazomyne includes L-arginine, saw palmetto, *Gingko biloba*, damiana, Polygonum multiflorum, nettle leaf, Muira puama.	39.99 $ per box; three-month supply for 99.98 $	Online suppliers (orders can be placed by fax, phone, and mail too); Ebay.; Amazon (currently not available).	Presented as: "natural; money back guarantee; customers testimonials."	Ingredients are not fully listed nor explained in details; "It should not be taken in case of heart or thyroid problems; will not increase penis size."

Urological Association (AUA) has concluded that the data available on Yohimbine do not allow it to be recommended as standard treatment in erectile dysfunction particularly not in organic aetiology [29]. International Society for Sexual Medicine (ISSM) Standards Committee has recently stated "*if yohimbine has any potential indications for use in ED management, it would be among nonorganic ED; apart from ED, yohimbine has shown a limited efficacy in the treatment of premature ejaculation*" [21].

3.1.5. Safety. The side effects of yohimbine include high blood pressure, increased heart rate, manic reactions, bronchospasm, palpitations, insomnia, anxiety, irritability, shivering, sweating, nausea, flushing, and headaches which all can be attributed to its central adrenergic activity [26, 30].

3.1.6. Case Reports Concerning Safety of Yohimbine. Adverse events mostly due to self-administration of yohimbine have been reported since 1980s. In 1993, Sandler and Aronson have described the development of progressive renal failure, cutaneous eruption, and a lupus-like syndrome in a 42-year-old Afro-American man following yohimbine use [31]. Myers has reported a case of refractory priapism in a 42-year-old HIV infected and depressed man who self-administered a product containing yohimbine to treat his erectile dysfunction and was subsequently admitted to emergency department with a 20-hour lasting erection which required insertion of a proximal corpus cavernosum to spongiosum shunt (Quackles shunt) [32]. According to California Poison Control System, 238 cases of adverse reactions after yohimbine consumption have been identified within a 7-year period (2000–2006): most commonly reported adverse events have been gastrointestinal distress, tachycardia, anxiety, agitation, and hypertension [33]. US National Institute of Health also warns consumers about taking yohimbine supplements if they suffer from schizophrenia, anxiety, depression, or posttraumatic stress disorder [34]. Additional situation of emergency has been reported in Amman where the public corporation of the food and the medicine warned the citizens about the use of some unlicensed sexual stimulants, such as yohimbine, for its inclusion of poisonous substance strychnine that caused convulsions, hallucinations, and heart and kidney failure [35]. More recently, Yohimbine was detected in a product labelled as OxyELITE Pro and sold online as slimming pills. This caused the hospitalisation of two female patients aged 34 and 21 in Hong Kong for acute hepatitis symptoms. As a result, the Department of Health opened an investigation and appealed to members of the public not to buy or consume the product [30].

3.1.7. Psychological Safety. As mentioned above, anxiety and agitation are among the most common side effects of yohimbine or yohimbine-containing products [33]. US National Institute of Health warns consumers about taking yohimbine or Yohimbe supplements with some of the antidepressants and antipsychosis drugs: "*People should not combine Yohimbe with monoamine oxidase (MAO) inhibitors as effects may be additive. Yohimbe should be used with caution when taken with medicines for high blood pressure, tricyclic antidepressants, or phenothiazines (a group of medicines used mostly for mental health conditions such as schizophrenia). People with kidney problems and people with psychiatric conditions should not use Yohimbe*" [34]. In 1985, Linden et al. have reported a case of a 16-year-old girl who experienced an acute dissociative reaction accompanied by weakness, paraesthesia, incoordination, anxiety, headache, and chest pain after the ingestion of an aphrodisiac called "*yo-yo,*" which has been later identified as yohimbine [36]. Acute neurotoxic effects related to the ingestion of yohimbine-containing products have been reported by Giampreti et al., who has reported the case of a 37-year-old bodybuilder presented with malaise, vomiting, loss of consciousness, and repeated seizures after ingestion of 5 g of yohimbine during a competition [37].

3.2. Maca

3.2.1. Source and Preparations. Maca *(Lepidium meyenii)* is a Peruvian plant, which belongs to the Brassicaceae family. It grows in central Andes at more than 4000 m altitude; it is constituted of a flat overground portion and underground hypocotyl and roots. Hypocotyl colour allows the distinction of three different varieties: white, yellow, and black maca. Naturally dried hypocotyls have been used for centuries by native Andean populations as aphrodisiac, energizer, and enhancers of fertility and sexual function [38]. With the advent of Internet, maca has become a common ingredient of sexual enhancer products available worldwide.

3.2.2. Active Ingredients and Mechanism of Action. Maca extracts have been shown to contain benzyl glucosinolates and polyphenols, (1R,3S)-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCA), and p-methoxybenzyl isothiocyanate among many other chemicals [39]. The mechanism of action of maca in altering sexual behaviour is unknown.

3.2.3. Pharmacokinetics. No information could be found related to the pharmacokinetics properties of Maca.

3.2.4. Efficacy. Zheng et al. reported increased sexual behaviour in male rats and mice and decreased latency to erection in testes-removed rats following oral administration of lipid extracts of maca roots [40]. Cicero et al. demonstrated that sexual behavioural activity as well as locomotor activity was increased in rats treated with pulverised maca root orally [41]. In a further study, the same group has demonstrated that the hexanic extract of maca had more effect on sexual behaviour of rats than the methanolic and chloroformic extracts [42]. Lentz et al. measured ejaculatory and mounting behaviour and postejaculatory intervals in rats treated with maca orally for 30 days. They found that maca had only a small effect on sexual behaviour and locomotor activity but no effect on anxiety [43].

The studies with maca on human subjects were reviewed in 2010 [44]. Four randomised clinical trials met the authors' inclusion criteria: two trials suggested a significant positive

Table 2: Subjective reports of forums' users about sexual enhancers side effects.

Gingko biloba	(i) Head rush (ii) Anxiety (iii) Feeling of blood flowing through skin/feeling blood warming (iv) Tinnitus http://www.drugs-forum.com/forum/showthread.php?t=77902
	(i) Increased heart rate (ii) Dizziness (iii) Chest pain (iv) Phosphenes http://forum.lef.org/default.aspx?f=35&m=16405
	Anxiety and nausea (Ginkgo tea consumption while assuming clomipramine) http://www.socialanxietysupport.com/forum/f11/ginkgo-biloba-197737/
Maca	(i) Altered menstrual cycle (length modifications, anovulatory cycles) (ii) Painful intestinal cramps (iii) Severe gastritis (iv) Increased blood pressure (v) Moodiness http://archive.tcoyf.com/forums/t/119232.aspx
	(i) Increased heart rate (ii) Insomnia (iii) Depression/anxiety (iv) Worse premenstrual syndrome symptoms (v) Acne breakout http://www.highonhealth.org/what-nobody-tells-you-about-maca-root-powder-dangers-and-side-effects/
	Mood swings http://babyandbump.momtastic.com/pregnancy-tests/419834-gallery-o-tests-1075.html#post9282851
Horny goat weed	(i) Fever (ii) Increased heart rate (iii) Aggressiveness (iv) Irritability http://www.muscleandstrength.com/supplements/ingredients/horny-goat-weed.html#5

effect of maca on sexual dysfunction or sexual desire in healthy postmenopausal women [45] or healthy adult men [46], while the other trial failed to show any effects on healthy cyclists [47]. A further trial assessed the effects of maca in patients with erectile dysfunction using the International Index of Erectile Function Questionnaire and showed significant effects [48]. Lee et al. have reviewed the literature to determine maca's possible effects on menopausal symptoms and confirmed the inadequacy of the present data to clearly state efficacy and safety [49]. An overview of systematic reviews on various complementary medicine products for sexual dysfunction in elderly patients has found that the evidence for maca was insufficient [50].

3.2.5. Safety. Piacente et al. (2002) have shown the existence of 1R,3S-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCA) in the extracts of maca. MTCA has been suggested to be an inhibitor of the monoamine oxidase (MAO) enzyme and is a comutagenic or a precursor to mutagenic compounds [51]. Because of these potential mutagenic properties of MTCA, the French Agency for Sanitary Security warned consumers of powdered maca root about possible health risks from its ingestion [52]. These findings have been disputed by others based on the assumption that MTCA is deactivated during the boiling process of the maca roots [53]. MTCA-like compounds have also been suggested to be associated with craving behaviour, which is common in addictions [51]. Side effects subjectively reported by fora users were altered menstrual cycles, moodiness, cramps, gastritis, and insomnia (see Table 2).

3.3. Horny Goat Weed

3.3.1. Source and Preparations. *Epimedium* is a genus of plants of the Berberidaceae family, including more than 50 species. Among the most frequently used in sexual enhancer products are *Epimedium grandiflorum* and *Epimedium sagittatum*. *Epimedium grandiflorum* is commonly known as horny goat weed named after the legendary discovery of its aphrodisiac properties, attributed to a Chinese goat herder who noticed an increased sexual activity in his herd after they ate the plant's leaves [54], and sold online with various names including ViaXtreme, which also contains undeclared sildenafil [17].

3.3.2. Active Ingredients and Mechanism of Action. The active ingredient of horny goat weed has been suggested to be

icariin, a flavonol glycoside [55]. Icariin and its derivatives have been suggested to increase NO synthesis in the penis [56], inhibit PDE5 in cavernosal smooth muscle [57–59], have positive neurotrophic effect on nitrergic nerves [56], enhance smooth muscle proliferation [60], and decrease advanced glycation endproduct formation [60] and mimic endogenous androgens [61]. Icariin has also been suggested to have anti-inflammatory, antiosteoporotic, and neuroprotective properties [62–64].

3.3.3. Pharmacokinetics. Icariin has been shown to have low oral bioavailability, poor absorption, and short plasma half-life [65]. Because of these unfavourable pharmacokinetics profiles, liposome encapsulated formulations of icariin are being developed [66].

3.3.4. Efficacy. Although icariin has been shown to be efficacious in treatment of erectile dysfunction in aged [67], diabetic [68], and castrated [69] animal models, it has not been tested in any randomised clinical trial.

3.3.5. Safety. No long-term toxicity study has been conducted using horny goat weed (or icariin) in any animal species. Partin and Pushkin have presented a case of a 66-year-old man with a history of cardiovascular disease who, after two weeks of consumption of herbal sexual enhancer containing horny goat weed, was admitted to hospital with a new-onset tachyarrhythmia and hypomanic symptoms (sexual and verbal inappropriate behaviour, irritable mood, and hyperverbal speech). The patient needed to undergo an electric cardioversion and to be treated with a therapy based on olanzapine and lorazepam [70]. Metz et al. reported a case of a painful vasculitic rash in a 77-year-old man, who had started a treatment with *Ginkgo biloba* and horny goat weed tablets four days before. The man improved after three days as an inpatient, with the suspension of the herbal supplement [71].

3.3.6. Psychological Safety. As mentioned above, one case has been reported with hypomanic symptoms combined with tachyarrhythmia [70]. During the online monitoring of discussion fora, several cases of aggressive behaviour and irritability were noted (see Table 2).

3.4. Ginkgo biloba

3.4.1. Source and Preparations. *Ginkgo biloba* is a living fossil tree, belonging to Ginkgoaceae family. Typically grown in China, Ginkgo plants are tall, normally reaching 20–35 m of height, with fan-shaped leaves. The extracts obtained from Ginkgo leaves contain flavonoid glycosides (e.g., myricetin and quercetin) and terpenoids (e.g., ginkgolides and bilobalides) and have been used for centuries in traditional Chinese medicine, particularly for memory enhancement and blood flow improvement.

3.4.2. Active Ingredients and Mechanism of Action. The most commonly used *Ginkgo biloba* extract is EGb761, which contains flavonoid glycosides, mainly composed of kaempferol, quercetin glucorhamnoside esters, and terpenes of ginkgolides and bilobalides. These ingredients have been suggested to have the ability to inhibit MAO enzyme and uptake of certain neurotransmitters such as noradrenaline and serotonin in the central nervous system [72]. A recent meta-analysis of 28 clinical studies with Ginkgo has found no significant effect on cognitive function [73]. Ginkgo extracts have been suggested to improve sexual function by improving the blood flow to the brain as well as to the genital organs. These extracts have also been suggested to increase NO bioavailability, which may have positive impact on sexual function [74].

3.4.3. Pharmacokinetics. Extracts of Ginkgo are a mixture of substances with a wide variety of physical and chemical properties and activities. A recent review on the pharmacokinetic properties of these substances concluded that the available pharmacokinetic data are rare and more studies need to be conducted [75]. It is generally accepted that Ginkgo extract is well absorbed in humans, rats, and rabbits after oral administration [75].

3.4.4. Efficacy. Ginkgo extracts have been tested as a treatment for antidepressant-induced sexual dysfunction, which is a common side effect in depressive disorder therapy, especially when using selective serotonin reuptake inhibitors (SSRIs). Despite the initial positive effect on sexual function based on various case reports [76], two randomised placebo controlled trials have found no significant benefit on sexual function with Ginkgo extracts [77, 78]. Although Ginkgo extracts have been suggested for the treatment of female sexual arousal disorders [79], no placebo controlled randomised trial has been reported.

3.4.5. Safety. A recent long-term study by National Toxicology Program has demonstrated that oral administration of Ginkgo extract caused cancer of thyroid gland and liver, atrophy of the olfactory epithelium, nephropathy, and mononuclear cell leukaemia in rats and mice [80]. One of the major ingredients, quercetin, is a known mutagen [81]. In reviews of the efficacy and safety of Ginkgo extracts in human subjects, no serious side effects were reported in clinical trials and side effects were similar to those seen in the placebo groups [82]. Ginkgo extract has been suggested to affect platelet aggregation, which may not only be useful in prevention of pathological events as thrombosis, but may also cause spontaneous bleeding in healthy individuals or patients treated with anticoagulants such as warfarin and aspirin [83]. There have been case reports of subdural hematoma or cerebral haemorrhage with headache, confusion, blurred vision, nausea, and vomiting after Ginkgo administration [84]. Some Ginkgo extracts may contain 4′-O-methylpyridoxine, which is a neurotoxin also known as "ginkgotoxin." Ginkgotoxin poisoning is characterised by epileptic convulsions, vomiting, unconsciousness, and irritability, which may be fatal if not promptly treated [85].

3.4.6. Psychological Safety. Ginkgo may interact with other medications particularly those acting on the central nervous system. It may decrease (alprazolam, citalopram, and diazepam) or increase (clozapine, methadone, olanzapine, and fluvoxamine) effects and side effects of such drugs; it may also induce hypomanic symptoms when taken together with St. John's wort, fluoxetine, and melatonin [86]. Anxiety was the most common psychological effect reported by Ginkgo users at Internet discussion fora (see Table 2).

3.5. Other Substances. Velvet antler has been used in traditional Chinese medicine for centuries, mainly as an energizer and to treat joint pain, cardiovascular diseases, and impotence. The name refers to the velvety skin covering growing antlers of male elk, deer, and moose, which can be removed with no harm for the animal. In western countries, elks and deer are anesthetized with xylazine or lidocaine before having velvet removed; this practice had determined an ethical controversy among veterinarians, to find balance between animal welfare and food safety (not being known drugs' withdrawal time for velvet) [87]. The most relevant issue currently identified for elk or deer velvet antler consumption is related to an infectious neurodegenerative prion disease known as chronic wasting disease (CWS). The core symptoms of this encephalopathy are notable weight loss and behavioural abnormalities (e.g., progressive hyperexcitability) [88]. Though currently interspecies transmission has not been yet demonstrated, the presence of CWS prions in animal muscle, fat, glands, and antler velvet may expose humans to infection by handling or consumption of diseased cervids products [89, 90]. No psychoactive properties have been yet demonstrated for velvet antler.

Turnera diffusa, also known as "damiana," is a small shrub common in Mexico, Central and South America, and the Caribbean. *Turnera diffusa* leaf is traditionally thought to be stimulant, aphrodisiac, tonic, diuretic, laxative, and useful to treat menstrual and pregnancy disorders [91]. Aphrodisiac and psychoactive properties have been ascribed for centuries to damiana. Its leaves are usually boiled to make an infusion with the aim of intensifying sexual sensations; moreover, when smoked, damiana leaves may produce similar effects to marijuana [92]. It has recently been found in products advertised on the Internet to increase sensuality, especially among women [16], as legal and safer alternative to *Cannabis* and sold as "mystical incenses" [93, 94]. These also often contain synthetic cannabinoids such as JWH-18, JWH-73, and HU210 that may cause severe intoxication and death [95, 96].

Nymphaea caerulea is a lotus flower belonging to Nymphaeaceae family. It is also known as "Blue Water Lily" or "Egyptian Lotus" and it is sold as a powder named "Blue Lotus." The flower has been used by ancient Egyptians not only to enhance sex drive and to improve sexual performance, but also to stimulate blood flow and as an antiageing treatment. It has also recreational potential when added to wine or smoked, due to its psychoactive properties [97]. The flower may indeed induce both narcotic and euphoric effects and, if taken in large amounts, may cause slightly hallucinogenic symptoms [98].

Ptychopetalum olacoides (*Muira puama*), also called "potency wood," grows primarily in Brazil. Popular belief claims that it can improve sexual function especially in old men [7]. This herb may be found in plant markets or in herbal formulations, usually sold to increase physical, mental, and/or sexual performance. Few clinical studies have so far examined the prosexual effects of *Muira puama*. Waynberg reported in 1994 that 60% of men with low libido have reported increased sexual desire and 50% of men with poor erection have reported improved erectile function following *Muira puama* administration [99]. Another study has shown that *Muira puama* improved sexual desire, sexual fantasies, and the ability to achieve orgasm in 65% of women with prior sexual dysfunction [100].

3.5.1. Synthetic Substances. Among synthetic substances used as sexual enhancers, well-known examples include MDPV (methylenedioxypyrovalerone), known as "Ivory Wave," 2C-B, and mephedrone (4-methylmethcathinone), also called with the nickname of "Miaow Miaow." The aforementioned substances have stimulating and aphrodisiac properties similar to amphetamines and MDMA ("Ecstasy"). Because of their partially synthetic and partially natural composition, some sexual enhancer substances are defined "mixed." Lust is a stimulant made up of *Sida cordifolia* extract. This plant contains L-ephedrine, which is a natural amphetamine acting on both central and peripheral nervous systems. The effects of L-ephedrine are mainly linked to an expansion of sexual perception [101]. Another component of Lust is saw palmetto (*Serenoa repens*, *Serenoa serrulata*), another natural aphrodisiac; the plant's berries are used to increase muscular power and libido. The last Lust component is L-arginine, an amino acid believed to have positive effects on impotence and infertility [102].

4. Discussion and Conclusions

The exponential increase in the use of unlicensed sexual enhancing products, often characterized by the undeclared presence of psychoactive agents, represents a serious challenge both from clinical and public health point of view, despite their large and uncontrolled distribution on the Internet, including e-commerce websites (Ebay, Amazon). It has been estimated that approximately six million men in the EU purchase these products from the Internet [103]. Possible reasons behind such a risky behaviour include (a) the embarrassment to speak with a doctor, (b) the thought that buying them online would be the fastest and cheapest way to solve the problem, (c) curiosity, (d) peer-pressure, and (e) the increase of sexual confidence and performance [5].

In a performance-based society, the e-commerce of food and herbal supplements sold for sexual enhancing purposes is becoming a highly profitable market as a result of low-cost manufacturing capacity in countries such as China and India as well as the globalization of free trade and the Internet as a platform for rapid distribution [94, 103, 104]. In this context, unscrupulous manufacturers/retailers are exploiting

the common belief that "natural" products are healthier alternatives to pharmaceutical treatments and infiltrate undeclared harmful psychoactive substances in their products [5]. This represents a growing public health threat, which is putting the population at risk. The frequent occurrence of side effects and the potential induction of symptoms of psychiatric interest, such as mood elevation, anxiety, hallucinations, and other psychotic symptoms, are issues that need to be clarified and constantly monitored at the international level [105, 106]. The possible impact on subjects with psychiatric disorders, usually at risk for sexual disjunctions and therefore possible consumers, may be devastating.

Sexual function is closely related to the function of the central nervous system; it is therefore not surprising that psychological and psychiatric disorders are closely associated with sexual dysfunction [107]. For example, depression can be a cause or result of erectile dysfunction. Some of the antidepressants can also cause sexual dysfunction. It is therefore essential that patients with sexual dysfunction either of psychogenic or organic aetiology should avoid taking such herbal products which may have adverse effects on their mental state. Similarly, patients taking centrally acting medications such as antidepressants or antipsychotics should avoid using such products which may cause unwanted herb-drug interactions and hence side effects, one of which may be sexual dysfunction.

In addition, there is still a distinct paucity of evidence-based and up-to-date information available for medical professionals on the effects and risks associated with the consumption of these products. In this sense, the use of unstructured, free, and near real-time sources of information such as Internet news and online reports is essential to rapidly acquire and share knowledge and understanding of the rapidly changing drug market and be better prepared to face this new challenge globally.

A limitation of this study was that only publicly available websites and similar sources were monitored. In order to improve the coverage of the study, not only the websites but also more private ways of communication (including newsgroups, chat rooms, mailing lists, social networking, e-newsletters, bulletin boards, and videos) were monitored. Because some of the discussion fora have restricted access to non-registered members, a comprehensive quantitative analysis could not always be fully performed. A further limitation may be that the present findings do rely mostly on what is reported by users. We did not have any possibility to ascertain whether the substance the online alleged drug users were taking was only a sexual stimulant or a combination of various products.

Considering the fact that only less than 1% of the side effects are reported for herbal products, it is concerning to find the variety of psychological symptoms disclosed by the users in online discussion fora, which may only be a fraction of the tip of an iceberg. In conclusion, the four substances, yohimbine, maca, horny goat weed, and *Ginkgo biloba,* commonly found in sexual enhancement products carry potential safety risks particularly in psychological context. The users, physicians, and regulators should be aware of these risks.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

[1] S. A. Pratap and S. Rajender, "Potent natural aphrodisiacs for the management of erectile dysfunction and male sexual debilities," *Frontiers in Bioscience*, vol. 4, pp. 167–180, 2012.

[2] N. Campbell, J. P. Clark, V. J. Stecher et al., "Adulteration of purported herbal and natural sexual performance enhancement dietary supplements with synthetic phosphodiesterase type 5 inhibitors," *Journal of Sexual Medicine*, vol. 10, no. 7, pp. 1842–1849, 2013.

[3] S. L. Kenyon, J. Button, P. Perella, D. A. McKeown, and D. W. Holt, "An herbal remedy for impotence: more than was bargained for," *Journal of Clinical Pharmacology*, vol. 46, no. 11, pp. 1379–1381, 2006.

[4] B. J. Venhuis, M. E. Zwaagstra, J. D. J. van den Berg et al., *Illicit Erectile Dysfunction Products in the Netherlands. A Decade of Trends and a 2007–2010 Product Update*, National Institute for Public Health and the Environment, 2011.

[5] M. Evans-Brown, J. McVeigh, C. Perkins, and M. A. Bellis, *Human Enhancement Drugs: The Emerging Challenges to Public Health*, North West Public Health Observatory, 2012.

[6] S. Balayssac, V. Gilard, C. Zedde, R. Martino, and M. Malet-Martino, "Analysis of herbal dietary supplements for sexual performance enhancement: first characterization of propoxyphenyl-thiohydroxyhomosildenafil and identification of sildenafil, thiosildenafil, phentolamine and tetrahydropalmatine as adulterants," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 63, pp. 135–150, 2012.

[7] R. Shamloul, "Natural aphrodisiacs," *Journal of Sexual Medicine*, vol. 7, no. 1, pp. 39–49, 2010.

[8] E. Ernst, "Harmless herbs? A review of the recent literature," *The American Journal of Medicine*, vol. 104, no. 2, pp. 170–178, 1998.

[9] S. Bent and R. Ko, "Commonly used herbal medicines in the United States: a review," *The American Journal of Medicine*, vol. 116, no. 7, pp. 478–485, 2004.

[10] Adverse event reporting for dietary supplements: An inadequate safety valve. OEI-01-00-00180. Office of the Inspector General, HHS, 2001. 2001.

[11] P. G. Shekelle, M. L. Hardy, S. C. Morton et al., "Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis," *Journal of the American Medical Association*, vol. 289, no. 12, pp. 1537–1545, 2003.

[12] M. Keller, M. Blench, H. Tolentino et al., "Use of unstructured event-based reports for global infectious disease surveillance," *Emerging Infectious Diseases*, vol. 15, no. 5, pp. 689–695, 2009.

[13] W. Blaschek, S. Ebel, E. Hackenthal et al., *Hagers Handbuch der Drogen und Arzneistoffe*, Springer, Heidelberg, Germany, 2007.

[14] J. M. Betz, K. D. White, and A. H. der Marderosian, "Gas chromatographic determination of yohimbine in commercial yohimbe products," *Journal of AOAC International*, vol. 78, no. 5, pp. 1189–1194, 1995.

[15] GPHIN, Syntrax contains the female qualm of sexual impotence medicine weight loss looking at acute disease, Communication from Hong Kong, 2009.

[16] GPHIN, Again feel the woman! Communication posted on 2012/05/15 from Russia, 2012.

[17] GPHIN, FDA warns on sex, diet pills, communication posted on 2012/03/07 from South Florida Sun-Sentine, United States, 2012.

[18] GPHIN, Open once strong medicine contains hazardous wastes. The bureau appeals to sanitary science to stop use, Singapore, 2010.

[19] M. R. Goldberg and D. Robertson, "Yohimbine: a pharmacological probe for study of the α2-adrenoreceptor," *Pharmacological Reviews*, vol. 35, no. 3, pp. 143–180, 1983.

[20] A. Y. W. Chang, C.-M. Huang, J. Y. H. Chan, and S. H. H. Chan, "Involvement of noradrenergic innervation from locus coeruleus to hippocampal formation in negative feedback regulation of penile erection in the rat," *Hippocampus*, vol. 11, no. 6, pp. 783–792, 2001.

[21] H. Porst, A. Burnett, G. Brock et al., "SOP conservative (Medical and Mechanical) treatment of erectile dysfunction," *Journal of Sexual Medicine*, vol. 10, no. 1, pp. 130–171, 2013.

[22] U. Simonsen, D. Prieto, M. Hernández, I. Sáenz De Tejada, and A. García-Sacristán, "Prejunctional α2-adrenoceptors inhibit nitrergic neurotransmission in horse penile resistance arteries," *Journal of Urology*, vol. 157, no. 6, pp. 2356–2360, 1997.

[23] J. A. Owen, S. L. Nakatsu, J. Fenemore, M. Condra, D. H. C. Surridge, and A. Morales, "The pharmacokinetics of yohimbine in man," *European Journal of Clinical Pharmacology*, vol. 32, no. 6, pp. 577–582, 1987.

[24] S. W. Tam, M. Worcel, and M. Wyllie, "Yohimbine: a clinical review," *Pharmacology and Therapeutics*, vol. 91, no. 3, pp. 215–243, 2001.

[25] S. K. Guthrie, M. Hariharan, and L. J. Grunhaus, "Yohimbine bioavailability in humans," *European Journal of Clinical Pharmacology*, vol. 39, no. 4, pp. 409–411, 1990.

[26] Federal Institute for Risk Assessment, 2013, http://ec.europa.eu/food/food/labellingnutrition/vitamins/sa_yohimbe_en.pdf.

[27] E. Ernst and M. H. Pittler, "Yohimbine for erectile dysfunction: a systematic review and meta-analysis of randomized clinical trials," *Journal of Urology*, vol. 159, no. 2, pp. 433–436, 1998.

[28] A. A. Adeniyi, G. S. Brindley, J. P. Pryor, and D. J. Ralph, "Yohimbine in the treatment of orgasmic dysfunction," *Asian Journal of Andrology*, vol. 9, no. 3, pp. 403–407, 2007.

[29] D. K. Montague, J. P. Jarow, G. A. Broderick et al., "Chapter 1: the management of erectile dysfunction: an AUA update," *The Journal of Urology*, vol. 174, no. 1, pp. 230–239, 2005.

[30] GPHIN, Public urged not to buy or use slimming products with undeclared and banned drug ingredients, communication posted on 2013/06/05 from Hong Kong Government, 2013.

[31] B. Sandler and P. Aronson, "Yohimbine-induced cutaneous drug eruption, progressive renal failure, and lupus-like syndrome," *Urology*, vol. 41, no. 4, pp. 343–345, 1993.

[32] A. Myers and F. Barrueto Jr., "Refractory priapism associated with ingestion of yohimbe extract," *Journal of Medical Toxicology*, vol. 5, no. 4, pp. 223–225, 2009.

[33] T. Kearney, N. Tu, and C. Haller, "Adverse drug events associated with yohimbine-containing products: a retrospective review of the California poison control system reported cases," *Annals of Pharmacotherapy*, vol. 44, no. 6, pp. 1022–1029, 2010.

[34] "National Center for Complementary and Alternative Medicine. Herbs at a glance: Yohimbe. [Internet]," 2007, http://nccam.nih.gov/health/yohimbe.

[35] GPHIN, Warning on of the use of sexual stimulants that contains a poisonous substance, communication posted on 2008/07/29 from Jordan (in Arabic), 2008.

[36] C. H. Linden, W. P. Vellman, and B. Rumack, "Yohimbine: a new street drug," *Annals of Emergency Medicine*, vol. 14, no. 10, pp. 1002–1004, 1985.

[37] A. Giampreti, D. Lonati, C. Locatelli, L. Rocchi, and M. T. Campailla, "Acute neurotoxicity after yohimbine ingestion by a body builder," *Clinical Toxicology*, vol. 47, no. 8, pp. 827–829, 2009.

[38] G. F. Gonzales, "Ethnobiology and ethnopharmacology of *Lepidium meyenii* (Maca), a plant from the peruvian highlands," *Evidence-Based Complementary and Alternative Medicine*, vol. 2012, Article ID 193496, 10 pages, 2012.

[39] C. Clément, D. A. Diazgrados, B. Avula et al., "Influence of colour type and previous cultivation on secondary metabolites in hypocotyls and leaves of maca (*Lepidium meyenii* Walpers)," *Journal of the Science of Food and Agriculture*, vol. 90, no. 5, pp. 861–869, 2010.

[40] B. L. Zheng, K. He, C. H. Kim et al., "Effect of a lipidic extract from *Lepidium meyenii* on sexual behavior in mice and rats," *Urology*, vol. 55, no. 4, pp. 598–602, 2000.

[41] A. F. G. Cicero, E. Bandieri, and R. Arletti, "*Lepidium meyenii* Walp. improves sexual behaviour in male rats independently from its action on spontaneous locomotor activity," *Journal of Ethnopharmacology*, vol. 75, no. 2-3, pp. 225–229, 2001.

[42] A. F. G. Cicero, S. Piacente, A. Plaza, E. Sala, R. Arletti, and C. Pizza, "Hexanic Maca extract improves rat sexual performance more effectively than methanolic and chloroformic Maca extracts," *Andrologia*, vol. 34, no. 3, pp. 177–179, 2002.

[43] A. Lentz, K. Gravitt, C. C. Carson, L. Marson, and F. Giuliano, "Acute and chronic dosing of *Lepidium meyenii* (Maca) on male rat sexual behavior," *Journal of Sexual Medicine*, vol. 4, no. 2, pp. 332–340, 2007.

[44] B.-C. Shin, M. S. Lee, E. J. Yang, H.-S. Lim, and E. Ernst, "Maca (*L. meyenii*) for improving sexual function: a systematic review," *BMC Complementary and Alternative Medicine*, vol. 10, article 44, 2010.

[45] N. A. Brooks, G. Wilcox, K. Z. Walker, J. F. Ashton, M. B. Cox, and L. Stojanovska, "Beneficial effects of *Lepidium meyenii* (Maca) on psychological symptoms and measures of sexual dysfunction in postmenopausal women are not related to estrogen or androgen content," *Menopause*, vol. 15, no. 6, pp. 1157–1162, 2008.

[46] G. F. Gonzales, A. Córdova, K. Vega et al., "Effect of *Lepidium meyenii* (MACA) on sexual desire and its absent relationship with serum testosterone levels in adult healthy men," *Andrologia*, vol. 34, no. 6, pp. 367–372, 2002.

[47] M. Stone, A. Ibarra, M. Roller, A. Zangara, and E. Stevenson, "A pilot investigation into the effect of maca supplementation on physical activity and sexual desire in sportsmen," *Journal of Ethnopharmacology*, vol. 126, no. 3, pp. 574–576, 2009.

[48] T. Zenico, A. F. G. Cicero, L. Valmorri, M. Mercuriali, and E. Bercovich, "Subjective effects of *Lepidium meyenii* (Maca)

extract on well-being and sexual performances in patients with mild erectile dysfunction: a randomised, double-blind clinical trial," *Andrologia*, vol. 41, no. 2, pp. 95–99, 2009.

[49] M. S. Lee, B.-C. Shin, E. J. Yang, H.-J. Lim, and E. Ernst, "Maca (*Lepidium meyenii*) for treatment of menopausal symptoms: a systematic review," *Maturitas*, vol. 70, no. 3, pp. 227–233, 2011.

[50] E. Ernst, P. Posadzki, and M. S. Lee, "Complementary and alternative medicine (CAM) for sexual dysfunction and erectile dysfunction in older men and women: an overview of systematic reviews," *Maturitas*, vol. 70, no. 1, pp. 37–41, 2011.

[51] S. Piacente, V. Carbone, A. Plaza, A. Zampelli, and C. Pizza, "Investigation of the tuber constituents of maca (*Lepidium meyenii* Walp.)," *Journal of Agricultural and Food Chemistry*, vol. 50, no. 20, pp. 5621–5625, 2002.

[52] APSSA, "From the French Agency of Sanitary Security on foods relative to the risk assessment for health by consuming pulverized maca roots or as alimentary supplement," Afssa-Saisine 2004-SA-0155, 2004.

[53] G. F. Gonzales and C. Gonzales-Castañeda, "The methyltetrahydro-β-carbolines in Maca (*Lepidium meyenii*)," *Evidence-Based Complementary and Alternative Medicine*, vol. 6, no. 3, pp. 315–316, 2009.

[54] Horny Goats Weed [Internet] 2013, http://www.herbwisdom.com/herb-horny-goats-weed.html.

[55] J. J. Liu, S. P. Li, and Y. T. Wang, "Optimization for quantitative determination of four flavonoids in *Epimedium* by capillary zone electrophoresis coupled with diode array detection using central composite design," *Journal of Chromatography A*, vol. 1103, no. 2, pp. 344–349, 2006.

[56] A. W. Shindel, Z.-C. Xin, G. Lin et al., "Erectogenic and neurotrophic effects of icariin, a purified extract of horny goat weed (*Epimedium* spp.) in vitro and in vivo," *Journal of Sexual Medicine*, vol. 7, no. 4, pp. 1518–1528, 2010.

[57] Z.-C. Xin, E. K. Kim, C. S. Lin et al., "Effects of icariin on cGMP-specific PDE5 and cAMP-specific PDE4 activities," *Asian Journal of Andrology*, vol. 5, no. 1, pp. 15–18, 2003.

[58] Z. Jiang, B. Hu, J. Wang et al., "Effect of icariin on cyclic GMP levels and on the mRNA expression of cGMP-binding cGMP-specific phosphodiesterase (PDE5) in penile cavernosum," *Journal of Huazhong University of Science and Technology*, vol. 26, no. 4, pp. 460–462, 2006.

[59] H. Ning, Z.-C. Xin, G. Lin, L. Banie, T. F. Lue, and C.-S. Lin, "Effects of icariin on phosphodiesterase-5 activity in vitro and cyclic guanosine monophosphate level in cavernous smooth muscle cells," *Urology*, vol. 68, no. 6, pp. 1350–1354, 2006.

[60] J. Zhang, A.-M. Li, B.-X. Liu et al., "Effect of icarisid II on diabetic rats with erectile dysfunction and its potential mechanism via assessment of AGEs, autophagy, mTOR and the NO-cGMP pathway," *Asian Journal of Andrology*, vol. 15, no. 1, pp. 143–148, 2013.

[61] Z.-B. Zhang and Q.-T. Yang, "The testosterone mimetic properties of icariin," *Asian Journal of Andrology*, vol. 8, no. 5, pp. 601–605, 2006.

[62] B. Liu, H. Zhang, C. Xu et al., "Neuroprotective effects of icariin on corticosterone-induced apoptosis in primary cultured rat hippocampal neurons," *Brain Research*, vol. 1375, pp. 59–67, 2011.

[63] C. Shao-Rui, X. Xiang-Zhen, W. Yu-Hua et al., "Icariin derivative inhibits inflammation through suppression of p38 mitogen-activated protein kinase and nuclear factor-κb pathways," *Biological and Pharmaceutical Bulletin*, vol. 33, no. 8, pp. 1307–1313, 2010.

[64] R. Feng, L. Feng, Z. Yuan et al., "Icariin protects against glucocorticoid-induced osteoporosis in vitro and prevents glucocorticoid-induced osteocyte apoptosis in vivo," *Cell Biochemistry and Biophysics*, vol. 67, no. 1, pp. 189–197, 2013.

[65] L. Ye, J. Chen, and S. Liu, "Pharmacokinetics of icariin in rats," *Chinese Pharmaceutical Journal*, vol. 34, no. 1, pp. 33–36, 1999.

[66] W. Yang, X. C. Yu, X. Y. Chen, L. Zhang, C. T. Lu, and Y. Z. Zhao, "Pharmacokinetics and tissue distribution profile of icariin propylene glycol-liposome intraperitoneal injection in mice," *Journal of Pharmacology and Pharmacotherapeutics*, vol. 64, no. 2, pp. 190–198, 2012.

[67] M. N. Makarova, O. N. Pozharitskaya, A. N. Shikov, S. V. Tesakova, V. G. Makarov, and V. P. Tikhonov, "Effect of lipid-based suspension of *Epimedium* koreanum Nakai extract on sexual behavior in rats," *Journal of Ethnopharmacology*, vol. 114, no. 3, pp. 412–416, 2007.

[68] T. Liu, H. Xin, W.-R. Li et al., "Effects of icariin on improving erectile function in streptozotocin-induced diabetic rats," *Journal of Sexual Medicine*, vol. 8, no. 10, pp. 2761–2772, 2011.

[69] W.-J. Liu, Z.-C. Xin, H. Xin, Y.-M. Yuan, L. Tian, and Y.-L. Guo, "Effects of icariin on erectile function and expression of nitric oxide synthase isoforms in castrated rats," *Asian Journal of Andrology*, vol. 7, no. 4, pp. 381–388, 2005.

[70] J. F. Partin and Y. R. Pushkin, "Tachyarrhythmia and hypomania with horny goat weed," *Psychosomatics*, vol. 45, no. 6, pp. 536–537, 2004.

[71] D. Metz, P. Weston, and D. Barker, "Case report of vasculitic rash induced by *Ginkgo biloba* and/or Horny Goat Weed," *BMJ Case Reports*, vol. 2009, Article ID bcr07.2008.0399, 2009.

[72] C. J. Fehske, K. Leuner, and W. E. Müller, "*Ginkgo biloba* extract (EGb761) influences monoaminergic neurotransmission via inhibition of NE uptake, but not MAO activity after chronic treatment," *Pharmacological Research*, vol. 60, no. 1, pp. 68–73, 2009.

[73] K. R. Laws, H. Sweetnam, and T. K. Kondel, "Is *Ginkgo biloba* a cognitive enhancer in healthy individuals? A meta-analysis," *Human Psychopharmacology*, vol. 27, no. 6, pp. 527–533, 2012.

[74] C. A. Schmitt and V. M. Dirsch, "Modulation of endothelial nitric oxide by plant-derived products," *Nitric Oxide—Biology and Chemistry*, vol. 21, no. 2, pp. 77–91, 2009.

[75] C. Ude, M. Schubert-Zsilavecz, and M. Wurglics, "*Ginkgo biloba* extracts: a review of the pharmacokinetics of the active ingredients," *Clinical Pharmacokinetics*, vol. 52, no. 9, pp. 727–749, 2013.

[76] D. MacKay, "Nutrients and botanicals for erectile dysfunction: examining the evidence," *Alternative Medicine Review*, vol. 9, no. 1, pp. 4–16, 2004.

[77] B.-J. Kang, S.-J. Lee, M.-D. Kim, and M.-J. Cho, "A placebo-controlled, double-blind trial of *Ginkgo biloba* for antidepressant-induced sexual dysfunction," *Human Psychopharmacology*, vol. 17, no. 6, pp. 279–284, 2002.

[78] D. Wheatley, "Triple-blind, placebo-controlled trial of *Gingko biloba* in sexual dysfunction due to antidepressant drugs," *Human Psychopharmacology*, vol. 19, no. 8, pp. 545–548, 2004.

[79] R. Mazaro-Costa, M. L. Andersen, H. Hachul, and S. Tufik, "Medicinal plants as alternative treatments for female sexual dysfunction: utopian vision or possible treatment in climacteric women?" *Journal of Sexual Medicine*, vol. 7, no. 11, pp. 3695–3714, 2010.

[80] National Institutes of Health, "Ntp technical report on the toxicology and carcinogenesis studies of *Ginkgo biloba* extract

(cas no. 90045-36-6)in f344/n rats and b6c3f1/n mice(gavage studies)," 184 p. NIH Publication No. 13-5920, 2013.

[81] A. A. Hardigree and J. L. Epler, "Comparative mutagenesis of plant flavonoids in microbial systems," *Mutation Research*, vol. 58, no. 2-3, pp. 231–239, 1978.

[82] J. Birks, E. V. Grimley, and M. Van Dongen, "*Ginkgo biloba* for cognitive impairment and dementia," *Cochrane Database of Systematic Reviews*, no. 4, Article ID CD003120, 2002.

[83] A. Fugh-Berman, "Herb-drug interactions," *The Lancet*, vol. 355, no. 9198, pp. 134–138, 2000.

[84] S. Bent, H. Goldberg, A. Padula, and A. L. Avins, "Spontaneous bleeding associated with *Ginkgo biloba*: a case report and systematic review of the literature," *Journal of General Internal Medicine*, vol. 20, no. 7, pp. 657–661, 2005.

[85] E. Leistner and C. Drewke, "*Ginkgo biloba* and ginkgotoxin," *Journal of Natural Products*, vol. 73, no. 1, pp. 86–92, 2010.

[86] National Institutes of Health, "MedlinePlus Herbs and Supplements: Ginkgo (*Ginkgo biloba* L.) [Internet]," 2013, http://www.nlm.nih.gov/medlineplus/druginfo/natural/333.html.

[87] B. E. Rollin, "An ethicist's commentary on animal welfare versus food safety in collecting antler velvet," *Canadian Veterinary Journal*, vol. 42, no. 5, pp. 330–331, 2001.

[88] E. S. Williams, "Chronic wasting disease," *Veterinary Pathology*, vol. 42, no. 5, pp. 530–549, 2005.

[89] R. C. Angers, T. S. Seward, D. Napier et al., "Chronic wasting disease prions in eik antler velvet," *Emerging Infectious Diseases*, vol. 15, no. 5, pp. 696–703, 2009.

[90] S. E. Saunders, S. L. Bartelt-Hunt, and J. C. Bartz, "Occurrence, transmission, and zoonotic potential of chronic wasting disease," *Emerging Infectious Diseases*, vol. 18, no. 3, pp. 369–376, 2012.

[91] S. Kumar, R. Madaan, and A. Sharma, "Pharmacological evaluation of bioactive principle of Turnera aphrodisiaca," *Indian Journal of Pharmaceutical Sciences*, vol. 70, no. 6, pp. 740–744, 2008.

[92] R. Arletti, A. Benelli, E. Cavazzuti, G. Scarpetta, and A. Bertolini, "Stimulating property of Turnera diffusa and Pfaffia paniculata extracts on the sexual behavior of male rats," *Psychopharmacology*, vol. 143, no. 1, pp. 15–19, 1999.

[93] GPHIN, Kazakhstan has forbidden import of smoking grassy mixes, communication posted on 2010/01/21 from Kazakhstan (in Russian), 2010.

[94] O. Corazza, S. Assi, P. Simonato et al., "Promoting innovation and excellence to face the rapid diffusion of novel Psychoactive substances in the EU: the outcomes of the reDNet project," *Human Psychopharmacology*, vol. 28, no. 4, pp. 317–323, 2013.

[95] F. Schifano, A. Ricciardi, O. Corazza et al., "New drugs and role of the web: psychonaut Web Mapping Project," *Rivista di Psichiatria*, vol. 45, no. 2, pp. 88–93, 2010.

[96] V. Auwärter, S. Dresen, W. Weinmann, M. Müller, M. Pütz, and N. Ferreirós, ""Spice" and other herbal blends: harmless incense or cannabinoid designer drugs?" *Journal of Mass Spectrometry*, vol. 44, no. 5, pp. 832–837, 2009.

[97] C. R. Ossian, "The Most Beautiful of Flowers (review of Water Lilies and Lotuses in ancient Egypt)," *KMT Magazine*, vol. 1, pp. 48–59, 1999.

[98] W. A. Emboden, "Transcultural use of narcotic water lilies in ancient Egyptian and Maya drug ritual," *Journal of Ethnopharmacology*, vol. 3, no. 1, pp. 39–83, 1981.

[99] J. Waynberg, "Yohimbine vs. muira puama in the treatment of sexual dysfunction," *The American Journal of Natural Medicine*, vol. 1, pp. 8–9, 1994.

[100] J. Waynberg and S. Brewer, "Effects of Herbal vX on libido and sexual activity in premenopausal and postmenopausal women," *Advances in Therapy*, vol. 17, no. 5, pp. 255–262, 2000.

[101] C. M. Meston and J. R. Heiman, "Ephedrine-activated physiological sexual arousal in women," *Archives of General Psychiatry*, vol. 55, no. 7, pp. 652–656, 1998.

[102] M. Scibona, P. Meschini, S. Capparelli, C. Pecori, P. Rossi, and G. F. Menchini Fabris, "L-arginine and male infertility," *Minerva Urologica e Nefrologica*, vol. 46, no. 4, pp. 251–253, 1994.

[103] "European monitoring centre for drugs and drug addictions," Annual Report on the State of the Drugs Problem in Europe, Lisbon, Portugal, 2012.

[104] GPHIN, Health food is contained forbidding medicine changing a name sell again and again, communication posted on 2010/07/28 from Taiwan, 2010.

[105] GPHIN, Nationwide Track and Trace System Urgently Needed, communication posted on 2013/07/01 from United States, 2013.

[106] F. Schifano, P. Deluca, L. Agosti, G. Martinotti, J. M. Corkery, B. Alex et al., "Psychonaut 2002 Research Group. New trends in the cyber and street market of recreational drugs? The case of 2C-T-7 ("Blue Mystic")," *Journal of Psychopharmacology*, vol. 19, no. 6, pp. 675–679, 2005.

[107] I. Sáenz de Tejada, J. Angulo, S. Cellek et al., "Pathophysiology of erectile dysfunction," *Journal of Sexual Medicine*, vol. 2, no. 1, pp. 26–39, 2005.

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Research Article

Individual Differences in Gambling Proneness among Rats and Common Marmosets: An Automated Choice Task

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Interest is rising for animal modeling of pathological gambling. Using the operant probabilistic-delivery task (PDT), gambling proneness can be evaluated in laboratory animals. Drawing a comparison with rats, this study evaluated the common marmoset (*Callithrix jacchus*) using a PDT. By nose- or hand-poking, subjects learnt to prefer a large (LLL, 5-6 pellets) over a small (SS, 1-2 pellets) reward and, subsequently, the probability of occurrence of large-reward delivery was decreased progressively to very low levels (from 100% to 17% and 14%). As probability decreased, subjects showed a great versus little shift in preference from LLL to SS reinforcer. Hence, two distinct subpopulations ("non-gambler" versus "gambler") were differentiated within each species. A proof of the model validity comes from marmosets' reaction to reward-delivery omission. Namely, depending on individual temperament ("gambler" versus "non-gambler"), they showed either persistence (i.e., inadequate pokes towards LLL) or restlessness (i.e., inadequate pokes towards SS), respectively. In conclusion, the marmoset could be a suitable model for preclinical gambling studies. Implementation of the PDT to species other than rats may be relevant for determining its external validity/generalizability and improving its face/construct validity.

1. Introduction

The emerging field of neuroeconomics is focused—by interdisciplinary approaches [1, 2]—on the ability of animals, including humans, to process multiple alternatives and to choose an optimal course of action. One of the major research areas in neuroeconomics is decision-making under risk and/or uncertainty (e.g., [3]). To know whether subjects will tend to seek or avoid risk under various circumstances (e.g., [4–7]) is mostly relevant for a number of economic activities, such as investment, speculation, and gambling (e.g., [8–10]).

Betting money represents a recreational activity for the majority of people, but it may become a serious, clinically relevant, behavioural disorder for others (DSM-IV-TR and DSM-V, [11–13]). Pathological gambling, which affects up to 5.3% of adult humans in western societies [14], is rapidly emerging as both a social and a health concern [15, 16]. Interest is therefore rising for animal modeling of gambling proneness. Indeed, evidence obtained on nonhuman subjects can inform the research on human pathological gambling in several ways (for a review, see [17]).

There has been increasing interest in the common marmoset (*Callithrix jacchus*, a species of New World monkeys) as a model for experiments in neuroscience. They have been used in different areas of biomedicine, including neurobiology [18, 19], toxicology [20, 21], and immunology [22, 23] and for the study of neurodegenerative disorders [24–28]. To our knowledge, there is only one study evaluating decision-making under uncertainty in common marmosets [10]. The task employed by these authors involved the choice between

two bowls (containing constant or risky reward): caps of different colors were indication of a nonrisky or risky choice. Similar settings, employing bowls and colored caps, were used for most of the experiments in nonhuman primates [29]. Very little is known about the possibility to run these probabilistic reward tasks, in nonhuman primates, by means of automated, operant panels. The present study aims at evaluating the potential of marmosets tested by means of automated, operant panels as an animal model for human (pathological) gambling.

Gambling proneness can be evaluated in laboratory settings using the probabilistic-delivery task (PDT), an operant protocol classically performed in rats [30–38]. The PDT is based on the choice between a "Small & Sure" (SS) and a "Large & Luck-Linked" (LLL) reward [39, 40]. After a basal preference for LLL is established, the probability that large-reward delivery actually occurs decreases progressively to very low levels. Thus, to maximize the payoff, subjects should be flexible enough to abandon their large-reward preference, previously developed. Since optimal performance is expressed by a choice-shift towards a small reward, this entails a self-control effort in order to overcome the "innate drive" that justifies LLL attractiveness [35–37]. By contrast, a sustained preference for a large but extremely rarefied reward denotes temptation to gamble. The unrewarded visits to the poking holes, expressed during the postchoice timeout interval, can also be measured. Such inadequate responding can be considered an index of frustration (i.e., restlessness or persistence; see Methods) due to the punishment (consisting in reward-delivery omission). An experimental apparatus, originally developed for rodents [41], has been recently adapted to the common marmoset [42]. In such a recent experiment, we showed that impulsive behaviour can be reliably modeled in a delayed-reward setting.

A landmark in the PDT protocol is the "indifferent" point, that is, the specific level of uncertainty at which the animals can choose either option freely with no effect on the overall economic convenience [34]. As an example, if the ratio between large and small reward size was 3- to 5-fold (as in the present study), then the indifferent point (at which either choice was mathematically identical in terms of total foraging) ranged from $p = 33\%$ to $p = 20\%$. This situation is depicted in Figure 1. We initially imposed a range of P values before the indifferent point (i.e., 100%, 50%) when LLL was always the optimal choice. Rats were then tested far beyond the indifferent point (i.e., 17%, 14%) when LLL became a suboptimal option and the economic benefit is attained unequivocally by choosing repeatedly the small-reward option.

This study aims (i) to evaluate marmosets as possible model for gambling proneness, using the PDT and drawing a comparison with rats, and (ii) to investigate interindividual differences as an approach to study the psychobiological bases and evolutionary roots of human gambling behaviour. Besides, the implementation of the PDT to species other than rats may be relevant for determining its external validity/generalizability and for improving its face/construct validity.

2. Materials and Methods

2.1. Ethical Note. All experimental procedures were approved by Institutional Animal Survey Board on behalf of the Italian Ministry of Health (licence to GL for rats and to AV for marmosets). Procedures were in close agreement with the European Communities Council Directive (86/609/EEC) as well as with Italian law (Italian Legislative Decree 116/92). As for marmosets, they were housed and cared for following the guidelines of both the Italian Association of Primatology and the International Primatological Society. All efforts were made to minimize animal suffering, to reduce the number of animals used, and to utilize alternatives to *in-vivo* techniques, if available.

2.2. Subjects and Housing

2.2.1. Rats. Twelve adult (mean bodyweight 381.3 ± 9.5 g) Wistar male rats (Charles River, Italy) were housed in pairs inside Makrolon-type III cages with sawdust bedding, kept in an air-conditioned room (temperature 21 ± 1°C, relative humidity 60 ± 10%), on a 12 h reversed light-dark cycle (lights off at 7.00 a.m.). Water was available *ad libitum*, whereas food (Altromin-R, A. Rieper S.p.A., Vandoies, Italy) was available *ad libitum* until the start of the experimental protocol. Food restriction, imposed by the experimenter through a limited quantity of extra-food given at the end of each experimental session, was applied to increase the animal's motivation to work for food delivery (see below for details).

2.2.2. Marmosets. Fifteen adult male and female common marmosets were involved in the present study. Each of the five family groups was housed in a home-cage measuring 80 × 130 × 220 cm. The floors of the cages were covered in wood shavings and each cage contained various forms of enrichment (including wooden branches, mobile objects, platforms, a wooden nest box, and other items) which were periodically changed. All families had auditory, olfactory, and partial visual contact with each other. One family at a time (on a daily rotation basis) was given access via tunnels to two other cages (experimental cages) of the same size as the home-cages, in an adjacent room. All rooms had a controlled temperature of 22 ± 1°C, a humidity of 50 ± 5%, and a 12-h light-dark cycle, with lights on at 6.00 a.m., which included exposure to UV-B lights. The diet consisted of specific commercial pellets for marmosets (Mucedola Ltd., Lecco, Italy), plus a portion of various fruits and vegetables. The monkeys were usually fed on a daily basis at approximately 9.00 a.m. whilst water and pellets were available *ad libitum*.

2.3. Apparatus

2.3.1. Rats. Computer-controlled operant chambers, made of aluminium and Plexiglas with grid floor (Coulbourn Instruments, Allentown, PA, USA), were placed in an experimental room, adjacent to the animal room. The operant chambers were provided (on a same wall) with two nose-poking holes, two chamber lights (placed over each

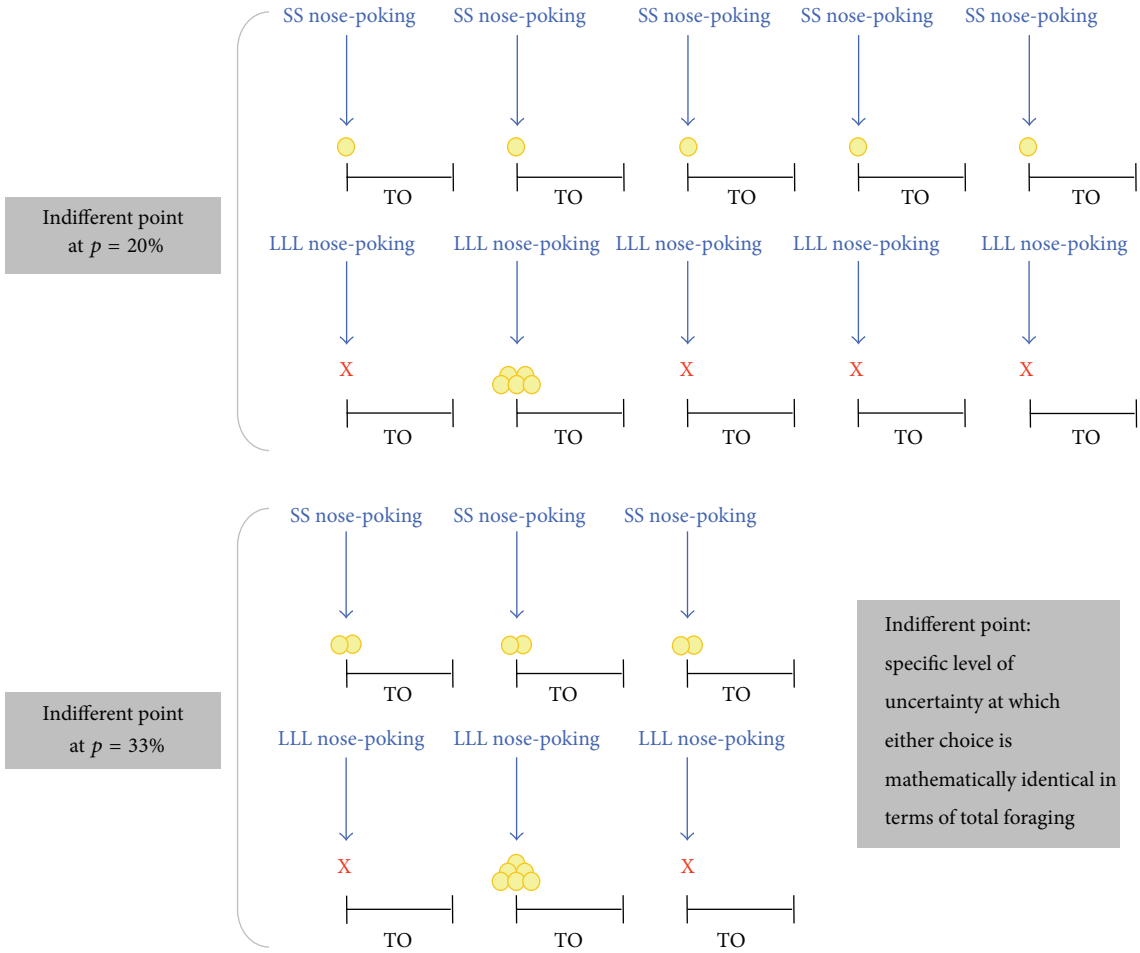

Figure 1: Schematic representation of the "indifferent" points. Arrows represent nose-poking tested under the PDT protocol: nose-poking in "Small & Sure" (SS) hole resulted in the certain delivery of 1-2 pellets, whereas nose-poking in "Large & Luck-Linked" (LLL) hole resulted in the delivery (or not) of 5-6 pellets, according to the level of probability "p," which was decreased progressively over days. Thus, if the ratio between large and small reward size was 5-fold (upper part of the scheme), then the indifferent point was at $p = 20\%$. By contrast, if the ratio between large and small reward size was 3-fold (lower part of the scheme), then the indifferent point was at $p = 33\%$. TO: timeout.

nose-poking hole), two feeder devices, and two food-magazines (each with a magazine light, signalling the length of the timeout, TO) where precision pellets (45 mg, F06555, Bio-Serv, Frenchtown, NJ, USA) were delivered. Nose-poking in either hole was detected by a photocell and was recorded by a computer (with custom-made software), which also controlled food delivery.

2.3.2. Marmosets. Two computer-controlled operant panels (45 × 30 × 15 cm; "HOPs", PRS Italia, Rome, Italy; [42]) were placed in each of the two experimental cages on a plywood platform (30 × 50 cm). The panels were provided with two hand-poking holes (one on each side), two purple hole lights above them, a single white house-light placed in the top middle of the panel, a feeder device, and two food-magazines (next to each hole with magazine lights) where precision pellets (45 mg, banana flavor, F0059, Bio-Serv, Frenchtown, NJ, USA) were delivered. The panels were connected through an interface to a computer, where software ("Sk020", PRS Italia, Roma, Italy; [42]) controlled and recorded all events. Hand-poking in either hole resulted in the differential delivery of pellets in the corresponding food-magazine (see below for details).

2.4. Experimental Procedure

2.4.1. Rats. After four weeks of habituation to the housing conditions and handling by the experimenters, rats were tested in the probabilistic-delivery (PD) task for gambling proneness, in the middle of the dark phase of their light-dark cycle (between 11.00 and 15.00 a.m.). Four chambers were used; each rat was tested daily in the same chamber at the same hour, five days a week. The total number of completed trials and the intertrial interval were not fixed, since rats were free to express nose-poking for food at their own, individually variable rate during the 25 min session.

After each daily session, rats were returned to their home-cage, where they were given an appropriate amount of

standard food (approximately 4.5 g each) to keep their body weight at 90% of their free feeding body weight.

2.4.2. Marmosets. The experimental sessions were performed between 9.00 and 13.00 a.m., five days a week. The total number of completed trials and the intertrial interval were not fixed, since marmosets were free to express hand-poking for food at their own, individually variable rate during the session. After the experimental session, in order to increase their motivation to work for food delivery on the following day, monkeys were fed at approximately 13.00 a.m., namely, after the experimental sessions had been completed, and received only small portions of fruit.

During the pretraining, training, and testing phases, two monkeys from the same family were tested simultaneously in the two opposite experimental cages, with their backs to each other. This was aimed to reduce the effects of social isolation. Before each session, panels remained covered with a wooden box until both subjects (selected to be tested) entered the experimental cages. At that point, the software was started and the wooden covers were removed. This was intended to prevent monkeys from interacting with the panels before they were turned on. Every day, at the end of the experimental sessions, the panels were again covered so that monkeys were free to move around the experimental cages without interacting with them.

Each session lasted 5 min, because the common marmoset has a relatively short attention span; attempts to use a longer testing time often made them loose interest in the apparatus.

2.5. Experimental Protocol

2.5.1. Rats

Training. During the training phase (3 days), nose-poking in one of the two holes resulted in the delivery of 1 to 2 pellets in the corresponding magazine, whereas nose-poking in the other hole resulted in the delivery of 5 to 6 pellets in the other magazine. After nose-poking and before food delivery, the chamber light above the nose-poked hole was turned on for 4 s. Following food delivery, the corresponding magazine light was turned on for 15 s (timeout, TO), during which additional nose-poking was recorded but was without scheduled consequences (i.e., inadequate). The magazine light was then turned off, and the system was ready for the next trial. These training sessions allowed all subjects to reach a significant preference for the large reward.

Testing. During the testing phase (7 days) a probabilistic dimension was associated with the delivery of the large reward. The chamber lights were switched on after nose-poking following the usual schedule. However, delivery of the large reward was sometimes omitted, according to a given level of probability (p = percentage of actual food delivery over total demands). The small-reward delivery was unchanged. Hence, animals had a choice between a "Large & Luck-Linked" (LLL) or a "Small & Sure" (SS) reward. The probability level was kept fixed for each daily session and was decreased progressively over days (from $p = 100\%$ to $p = 50\%$, $p = 33\%$, $p = 25\%$, $p = 20\%$, $p = 17\%$, and finally $p = 14\%$).

2.5.2. Marmosets

Training. Following familiarization and pretraining (see [42]), each monkey was placed individually in the experimental cage for the training phase (17 days). Hand-poking into one hole of the panel triggered the delivery of 1 to 2 pellets, whilst hand-poking into the other hole triggered the delivery of 5 to 6 pellets. The active session was indicated by the house light switched on (whilst the remaining lights were all off). After hand-poking, the house light was turned off and the purple hole light corresponding to the hand-poked hole was turned on for 2 s before food delivery. During and following food delivery, the corresponding magazine light was turned on for 6 s to signal the length of the timeout (TO), during which additional hand-poking was recorded but was without any scheduled consequences (i.e., inadequate). Then, the magazine light was turned off, the house light was turned on, and the system was ready for the next trial.

All monkeys but 2 (who had to be excluded from further testing for lack of interest in the apparatus) developed and displayed a preference for the large reward in this phase.

Testing. During the testing phase (21 days) a probabilistic dimension was associated with the delivery of the large reward. The purple hole lights were switched on after hand-poking following the usual schedule. However, delivery of the large reward was sometimes omitted, according to a given level of probability ("p" = percentage of actual food delivery over total demands). The small-reward delivery was unchanged. We intended to implement in monkeys the same rarefaction of large-reward delivery as in rats [34], with exactly the same progression except that three consecutive sessions were run for each level of "p."

2.6. Analysis of Data and Experienced "Odds". Three monkeys and one rat were excluded from data analysis as they failed to reach the inclusion criterion. The inclusion criterion (for both marmosets and rats) was defined as a preference for the large reward of more than 60% during the two sessions before the indifferent point [38–40, 42].

As a measure of gambling proneness, the dependent variable was the choice preference (%) for the LLL reward over total choices expressed. A sustained preference for the LLL reward may be an indication of gambling-prone behaviour [34–40]. As a general measure of motor impulsivity [42–45], the dependent variables were the average number of inadequate pokes per trial, calculated for each session, performed towards either the SS hole (i.e., restlessness) or the LLL hole (i.e., persistence). Restlessness values may be higher for subjects who, after poking into the LLL hole, start to ineffectively poke into the SS hole when the large-reward delivery is omitted. Such behaviour may be considered a motor consequence of an intolerance to uncertainty, namely, an index of motor impulsivity [42, 45]. On the contrary, persistence values may be higher for subjects who, after poking into the LLL hole, continue to ineffectively poke

into the LLL hole when the large-reward delivery is omitted. Such behaviour may be considered an index of motor perseveration or cognitive inflexibility [46]. The following dependent variables were also considered: number of pellets earned per minute, number of trials completed per minute, and experienced odds.

Odds are defined as the mean number of omitted large-reward deliveries (because of "unlucky" events in the PDT) before a successful delivery (i.e., a "lucky" event in the PDT). The relation between "p" level and odds value is mathematical: odds = $(1/p) - 1$ or $p = 1/(\text{odds} + 1)$. The present protocol employed a fully probabilistic generation of reward delivery versus omission, thus resulting in a totally random sequence of "lucky" versus "unlucky" trials. Therefore, a discrepancy likely appears between the "set" level of probability and the actually experienced rate of reinforcement, due to the stochastic fluctuations. Thus, for each session of the testing phase, we calculated the actually experienced "p" values for individual rats and marmosets (i.e., successful LLL/total LLL $\times 100$), and turned them into the corresponding "experienced odds" values (i.e., (1/experienced probability) − 1). We plotted (on y-axis) the percent LLL preference, shown by rats and marmosets at each session, against (on x-axis) either (a) the set "p" values, selected by the experimenter, or (b) the "experienced odds," once calculated. The latter was thus used to normalize percent LLL preference against an index of subjective impact of uncertainty. A logarithmic fit was also performed. Specifically, for each experimental rat or monkey, the slope of the preference-odds curve was calculated using Microsoft Excel functions, with Log (odds + 1) as x-axis and percent LLL choice as y-axis values.

On the basis of the median value of steepness of this preference-odds curve, we differentiated two distinct subpopulations [45, 47] in both rats and marmosets: a "non-gambler" one, which shifted quickly towards the SS hole (i.e., with a very steep slope), and a "gambler" one, with little or no shift. The median subject was assigned to the group to which its slope value was closest.

2.7. Statistical Analysis. Data were analyzed using repeated-measures analysis of variance (ANOVA). The general model was 2-level species × 2-level strategy × 7-level session, where species (rat *versus* marmoset) and strategy (the two subpopulations of gamblers *versus* non-gamblers) were a between-subject factor and session (the set probability per daily session) was a within-subject factor.

Statistical analysis was performed using Statview II (Abacus Concepts, CA, USA). Data are expressed as mean ± SEM. Significance level was set at $P \leq 0.05$; ns = not significant; all statistics are two-tailed. Multiple comparisons were performed with Tukey's honestly significant difference (HSD) test.

3. Results

3.1. Choice Preference (%) for the Large-Uncertain Reward. On the whole, all animals showed a shift in preference towards the SS reward as the level of uncertainty increased. The ANOVA yielded a main effect of session (session: $F(6,102) = 14.31$, $P < 0.001$), confirming a progressive reduction of LLL preference when moving from $p = 100\%$ to $p = 14\%$ in probability of reward delivery.

As expected, individual differences in the preference for LLL versus SS rewards emerged in both rats and monkeys, with the identification of two distinct subpopulations (strategy: $F(1,17) = 33.29$, $P < 0.001$): one with a nearly horizontal curve (i.e., "gamblers") and another with a very steep slope (i.e., "non-gamblers"). For both rats and marmosets, the "non-gamblers" showed a clear shift in preference from LLL to SS as the level of probability decreased. On the contrary, the "gamblers" maintained a significant attraction for LLL, even beyond the indifferent point, when LLL became a suboptimal option (strategy × session: $F(6,102) = 7.47$, $P < 0.001$; Figure 2).

Multiple post hoc analyses revealed a significant difference between "gambler" and "non-gambler" marmosets on the last 3 sessions (i.e., at $p = 20\%, 17\%, 14\%$) and between "gambler" and "non-gambler" rats on the last 2 sessions (i.e., at $p = 17\%, 14\%$).

3.2. Experienced Odds. The ANOVA yielded a main effect of session ($F(6,102) = 4.66$, $P < 0.001$), confirming a progressive increase of odds values when moving from $p = 100\%$ to $p = 14\%$. There were no main effects neither for strategy ($F(1,17) = 0.16$, $P = 0.690$ ns) nor for species ($F(1,17) = 2.22$, $P = 0.154$ ns) and no interactions as well (Ps > 0.484). No difference emerged as well in multiple post hoc comparisons. This profile confirms no differences in odds values actually experienced by the four experimental groups.

The absence of any difference implies that a similar proportion of "lucky" versus "unlucky" pokes was experienced by subjects of the four groups. In other terms, neither group was "luckier" than the other. Thus, "gambler" individuals (both for marmosets and for rats) did not choose the LLL hole because simply they were "luckier," but likely because of attraction to binge reward and/or insensitivity to its uncertainty. Vice versa, the "non-gamblers" preferred to shift towards the SS hole not because they were "unlucky" with LLL pokes, but likely because of sensitivity and hence aversion to uncertainty.

3.3. Number of Inadequate Pokes per Trial Towards the LLL Hole (i.e., Persistence). The inadequate responding (i.e., pokes performed during the TO interval, without any scheduled consequence) measures the reaction of subjects to punishment (consisting in reward-delivery omission) and can be considered an index of frustration.

At very low probability values, the "gambler" marmosets (but not rats) showed a significant increase in persistence, suggesting that they were still seeking for LLL during TO durations. This was reflected by significant interaction terms in the ANOVA (strategy: $F(1,17) = 14.55$, $P = 0.001$; species: $F(1,17) = 20.39$, $P < 0.001$; strategy × species: $F(1,17) = 5.80$, $P = 0.028$; strategy × session: $F(6,102) = 5.21$, $P < 0.001$; species × session: $F(6,102) = 2.43$, $P = 0.031$; species × strategy × session: $F(6,102) = 4.09$, $P = 0.001$, Figure 3). Accordingly, once the TO had elapsed, they maintained

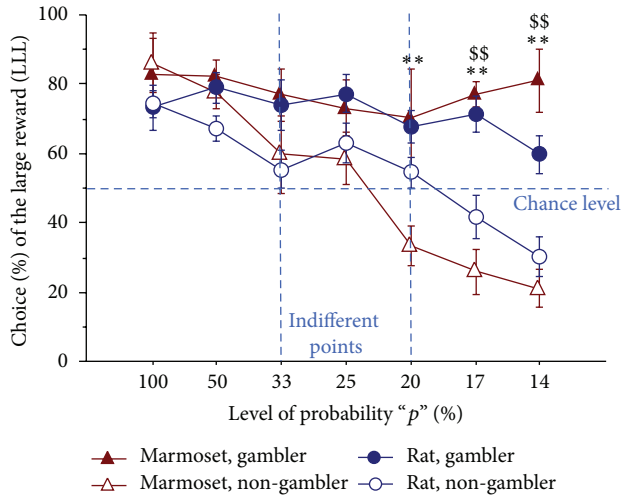

Figure 2: Gambling proneness: preference (%) for the LLL reward. Mean (±SEM) choice (%) of the large reward (LLL), shown by rats and marmosets belonging to the two distinct subpopulations ("gambler" versus "non-gambler", n = 5-6 per group). On the final "gambling" part of the testing phase, "non-gambler" individuals (both rats and marmosets) were progressively shifting towards a clear-cut SS preference. By contrast, in "gamblers" (both rats and marmosets), LLL preference remained significant, even beyond the indifferent point (when LLL became a suboptimal option). $^{**}P < 0.01$ gambler marmosets significantly different from non-gambler marmosets in post hoc test; $^{\$\$}P < 0.01$ gambler rats significantly different from non-gambler rats in post hoc test.

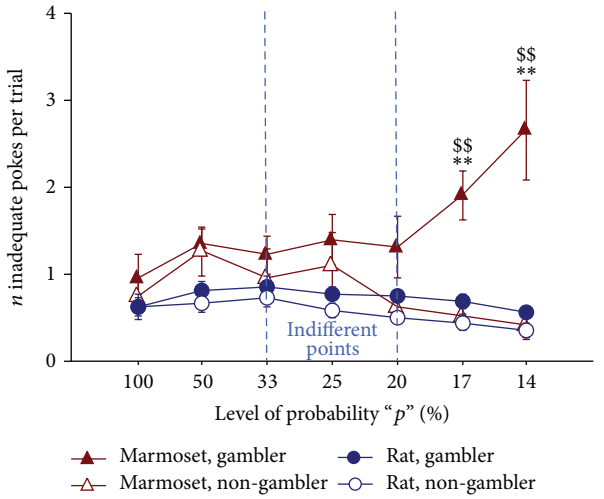

Figure 3: Persistence: number of inadequate pokes per trial towards LLL hole. Mean (±SEM) number per trial of LLL-inadequate pokes (i.e., performed during the postchoice TO interval, when they were without any consequence). Subjects are the same as in Figure 2. The "gambler" marmosets showed a significant increase in persistence at very low probability values, suggesting that they were still seeking for LLL during TO durations. $^{**}P < 0.01$ gambler marmosets significantly different from non-gambler marmosets in post hoc test; $^{\$\$}P < 0.01$ gambler marmosets significantly different from gambler rats in post hoc test.

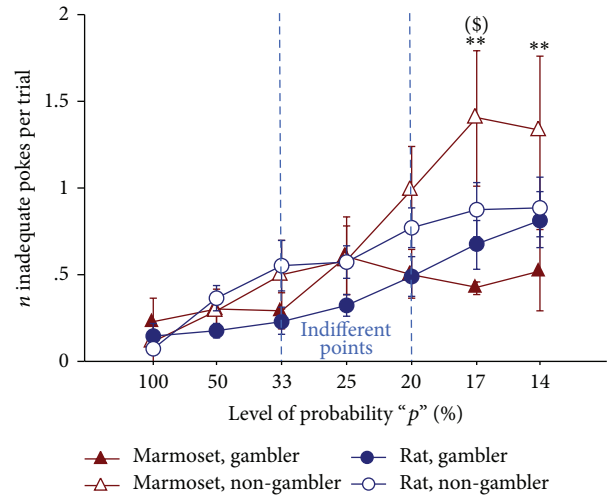

Figure 4: Restlessness: number of inadequate pokes per trial towards SS hole. Mean (±SEM) number per trial of SS-inadequate pokes (i.e., performed during the postchoice TO interval, when they were without any consequence). Subjects are the same as in Figure 2. While "non-gambler" marmosets showed a progressive increase of inadequate nose-pokes with decreasing levels of probability, "gambler" marmosets did not. Rats exhibited an intermediate profile. $^{**}P < 0.01$ gambler marmosets significantly different from non-gambler marmosets in post hoc test; $^{(\$)}0.05 < P < 0.1$ non-gambler marmosets significantly different from non-gambler rats in post hoc test.

a clear expression in their choice for LLL, a notion that supports the gambling-like profile of these animals.

Multiple post hoc comparisons evidenced, on the last 2 sessions (i.e., at p = 17%, 14%), that the "gambler marmosets" were showing the highest levels of persistence. In fact, a significant difference was found between "gambler marmosets," on one side, and "non-gambler marmosets" as well as "gambler rats," on the other hand.

3.4. Number of Inadequate Pokes per Trial Towards the SS Hole (i.e., Restlessness). Both rats and marmosets became overall more restless in the last sessions compared to the initial ones. Data are suggesting that, with progressive reward rarefaction, animals were increasingly disturbed by reward-delivery omission (session: $F(6,102) = 19.14$, $P < 0.001$).

This profile was particularly evident in "non-gambler" marmosets, who showed a progressive increase of uncertainty-induced restlessness, with decreasing levels of probability. By contrast, such inadequate responding was remarkably low in "gambler" marmosets, suggesting that these animals are less sensitive to uncertainty and relatively unaffected by reward loss. This was reflected by significant interaction terms in the ANOVA (strategy: $F(1,17) = 4.52$, $P = 0.048$; strategy × session: $F(6,102) = 3.33$, $P = 0.005$; species × strategy × session: $F(6,102) = 2.84$, $P = 0.014$, Figure 4).

Multiple post hoc comparisons evidenced the "non-gambler marmosets" as showing the highest levels of uncertainty-induced restlessness. In fact, we found a significant difference between "non-gambler" and "gambler"

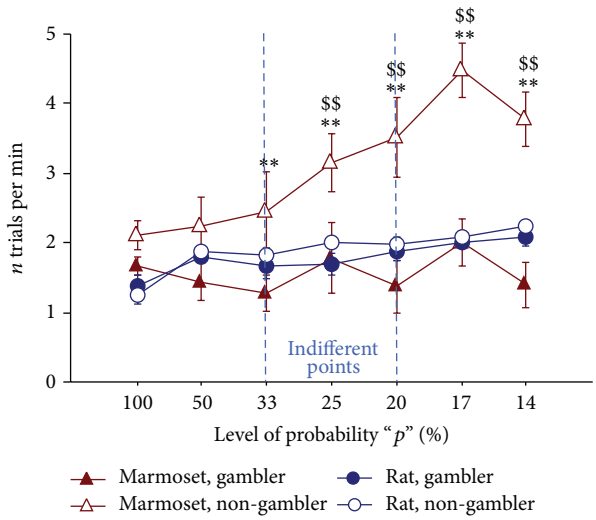

Figure 5: Trials per minute. Mean (±SEM) number of trials completed per minute. Subjects are the same as in Figure 2. A reaction to decreasing probability values was only shown by the "non-gambler marmosets," who increased the number of trials completed per minute to compensate for reward-delivery omission. $^{**}P < 0.01$ gambler marmosets significantly different from non-gambler marmosets in post hoc test; $^{\$\$}P < 0.01$ non-gambler marmosets significantly different from non-gambler rats in post hoc test.

marmosets on the last 2 sessions (i.e., at p = 17%, 14%) and, among the non-gambler subpopulation, a significant tendency ($0.05 < P < 0.1$) toward a difference between marmosets and rats on the penultimate session (i.e., at p = 17%).

3.5. Number of Trials Completed per Minute. Interestingly, the number of trials completed per minute increased markedly as the level of probability decreased, but only in uncertainty-aversive marmosets. By contrast, "gambler" marmosets apparently did not adapt their reward-seeking pokes to balance for increasing reward omission. Specifically, the ANOVA yielded a main effect of strategy ($F(1,17) = 15.96$, $P < 0.001$), of species ($F(1,17) = 5.69$, $P = 0.029$), of session ($F(6,102) = 13.83$, $P < 0.001$), and their interactions (strategy × species: $F(1,17) = 11.90$, $P = 0.003$; strategy × session: $F(6,102) = 4.74$, $P < 0.001$; species × session: $F(6,102) = 3.94$, $P = 0.001$; species × strategy × session: $F(6,102) = 3.81$, $P = 0.002$, Figure 5).

Multiple post hoc comparisons confirmed that the "non-gambler marmosets" were completing the highest number of trials per minute. In fact, we evidenced a significant difference between "non-gambler" and "gambler" marmosets on nearly all sessions (i.e., at p = 33%, 25%, 20%, 17%, and 14%) and between marmosets and rats of the "non-gambler" subpopulation on all of the same sessions but the third (i.e., at p = 25%, 20%, 17%, 14%).

3.6. Number of Pellets Earned per Minute. The total number of pellets delivered per minute was significantly higher in "non-gambler marmosets" than in the remaining groups

Table 1: Pellets per minute.

	p = 17%	p = 14%
Marmoset, gambler	2.69 ± 0.37	1.23 ± 0.66
Marmoset, non-gambler	7.84 ± 0.91	6.91 ± 0.89
Rat, gambler	2.79 ± 0.27	2.54 ± 0.32
Rat, non-gambler	3.15 ± 0.19	3.73 ± 0.26

Mean (±SEM) number of pellets earned per minute. Subjects are the same as in Figure 2. On final sessions at very low probability values (p = 17%, 14%), the amount of pellets obtained by "non-gambler" marmosets was considerably higher compared to "gambler" marmosets and rats of both subpopulations.

(strategy: $F(1,17) = 19.80$, $P < 0.001$; species: $F(1,17) = 9.61$, $P = 0.006$; strategy × species: $F(1,17) = 10.40$, $P = 0.005$). Pellets earned on average by "non-gambler marmosets" were 7.03 ± 0.47, compared with 3.57 ± 0.48 versus 3.62 ± 0.30 versus 4.17 ± 0.22 among "gambler marmosets," "gambler rats," and "non-gambler rats," respectively. The amount of pellets obtained by "non-gambler marmosets" was particularly higher at very low probability values (session: $F(6,102) = 41.40$, $P < 0.001$; strategy × session: $F(6,102) = 3.05$, $P = 0.009$; species × session: $F(6,102) = 5.80$, $P < 0.001$, Table 1).

Multiple post hoc comparisons evidenced, on final sessions, a significant difference between "non-gambler marmosets" on one side and "gambler marmosets" as well as "non-gambler rats" on the other hand (at p = 20%, 17%, 14%).

4. Discussion

The search for the psychobiological bases and evolutionary roots of human gambling behaviour has exploited different nonhuman animal species in probabilistic reward tasks. In addition to rats, largely investigated in our lab [34–40], other species like pigeons and starlings, for example, have been studied extensively [5, 48–51]. Of special interest are the studies conducted so far on nonhuman primates: lemurs [29], capuchin monkeys [52, 53], rhesus monkeys [4, 6, 7], orangutans and gorillas [54], as well as chimpanzees and bonobos [54, 55], have been utilized.

The aetiology of pathological gambling is multifactorial; both genetic (e.g., polymorphisms in the genes that code for serotonin and/or dopamine receptors and transporters) [56–58] and socioenvironmental (e.g., [59, 60]) risk factors have been identified. Moreover, irrational beliefs and distorted erroneous perceptions are thought to play a key role. Indeed, cognitive theories of gambling behaviour propose that expectancies of winning, erroneous beliefs about the intervention of luck, illusions of control, and subsequent entrapment do contribute to the development and the maintenance of gambling patterns [61–63]. One of the cognitive distortions regarding the outcome of a stake, thought to specifically confer vulnerability, is the so-called "near-miss effect" (i.e., the experience of "almost winning" [64–66]). By means of a novel model of slot machine play (the "rodent Slot Machine Task," rSMT), it has been recently demonstrated that rats are susceptible to this particular cognitive bias (i.e., putative-win signals in nonwinning trials [67]). Specifically, Winstanley and colleagues [67] found that (i) loss trials

that resemble wins ("near-misses") increased the behavioural expression of reward expectancy and that (ii) increased dopaminergic (DA) signalling (following administration of DA drugs) enhanced the expectation of reward delivery on loss trials. The latter may result from an inability to detect a negative prediction error (insensitivity to punishment) and/or from the generation of a positive reward expectancy [67].

The disruption of DA pathways significantly contributes to the propensity to gamble maladaptively [58]. With regard to the manifestation of the "near-miss effect," the DA system is thought to be mostly involved because of its role in signalling reward expectancy. It may be also relevant to mention that prolonged exposure to dopamine replacement therapy induces pathological gambling in a minority of patients with Parkinson's disease (PD, e.g., [68–70]). Interestingly, a recent study found that PD patients with pathological gambling (compared to control PD patients) showed, in the ventral striatum, lower dopamine transporter (DAT) expression and increased synaptic dopamine levels [69]. Similarly, mice with a permanent reduction of DAT functioning (DAT knockdown) exhibited increased preference for riskier options in the mouse Iowa gambling task (IGT; [71]). However, a gambling-prone profile in the PDT was found in rats following lentivirus-mediated DAT overexpression in nucleus accumbens [36, 37].

In the present study, as classically observed in previous studies on rats [34–40], all marmosets showed a shift in preference from LLL to SS as the level of probability decreased. Gambling proneness can then be identified by the steepness of the preference-probability curve. Two distinct subpopulations were differentiated within each species: a "non-gambler" one, which shifted quickly towards SS, and a "gambler" one, with little shift. On one side, "non-gambler" rats and marmosets clearly showed optimal performance, preferring the smaller, certain reward and decreasing their preference for the large reward as it became more and more uncertain. On the other hand, "gambler" rats and marmosets maintained a relatively stable preference for the large reward, despite a decreasing probability of its actual delivery.

Many factors may explain the development of such a suboptimal preference for a binge but largely uncertain reward. One factor is hyposensitivity to risk, whereby the subjects are unable to foresee (as they should) an uncertainty in the outcome (usually, a source of aversion before choice) or to perceive the punishment of "losses" (represented by a randomly and frequently omitted delivery of reward). A second factor is habit-induced rigidity, whereby subjects seem to behave according to a strongly consolidated choice strategy. Such form of inflexibility may be due to a failure of negative reinforcement, namely, a lack of feedback-reaction to the uncertainty-induced aversion and/or to the omission-related punishment, just described [17, 46].

Another set of factors is hypersensitivity to rewards: the binge size of the reward has an excessive motivational impact over the subjects and monopolizes their attention, regardless of any other characteristic of the reward itself. There is also the possibility that the internal states, elicited by the risk of "loss" and experienced under conditions of uncertainty, become attractive as a secondary, conditioned feature. This is because the large reward (which sooner or later is eventually delivered) may well be generating an overwhelming peak of positive reinforcement. Similarly, all the surrounding signals and cues, that accompany and predict the features of uncertainty, may themselves become secondary rewarding stimuli. Regardless of which of these factors prevails in the PDT, the suboptimal preference for a large, rarefied reward is considered an index of "gambling-proneness" [17, 46].

The inadequate responding (i.e., pokes performed during the TO interval, without any scheduled consequence) allows to evaluate the reaction of subjects to the punishment (consisting in reward-delivery omission). It should be noted that inadequate pokes are mainly performed during the postchoice TO interval that follows an "unlucky" poke into the LLL hole (when animals have no pellets to eat) and can be considered an index of frustration [38, 72]. Compared to rats, marmosets' reaction to reward-delivery omissions showed some interesting peculiarities; namely, depending on individual temperament ("gambler" versus "non-gambler"), they showed either persistence (i.e., inadequate pokes towards the LLL hole) or restlessness (i.e., inadequate pokes towards the SS hole), respectively. The "non-gambler" marmosets showed, with increasing levels of LLL rarefaction, a progressive increase of uncertainty-induced restlessness and intolerance. This result, suggesting that they were disturbed by frequent reward-delivery omission, is in agreement with their "uncertainty-averse" profile. By contrast, such inadequate, restless responding was remarkably low in "gambler" marmosets, suggesting these animals to be less sensitive to uncertainty and/or relatively unaffected by reward loss. Instead, the "gambler" marmosets showed a significant increase in persistence at very low probability values, suggesting that they were still seeking for LLL during TO durations which followed each omission. Accordingly, they maintained their choice for LLL, which was then expressed once the TO had elapsed, a notion that supports the gambling-like profile of these animals. Interestingly, we reported similar results in rats about the localization of inadequate nose-pokes [39]. We found that, during the final "gambling" part (i.e., sessions beyond the indifferent point), "gambler" rats performed inadequate nose-pokes mainly towards LLL hole. With progressive reward rarefaction, these animals were still seeking for the LLL reward during TO durations (and persisted in choosing the LLL hole once the TO had elapsed).

The lack of omission-induced frustration in "gambler" marmosets and rats may be related to the effectiveness of magazine lights as a secondary reinforcer. In fact, these lights were turned on even when delivery of the large reward was omitted. It may be proposed that reward omission was not properly perceived as punishment by these animals, in that the light cue alone could sustain choice behaviour. Magazine lights turned on in the absence of food could have a much higher, secondary reinforcing value, triggering an anticipated drive for bingeing and persistent LLL seeking. Like in second-order schedules [73], this cue-induced secondary reward may sustain continued responding in the LLL hole, even though

this implies a decreased overall foraging in the long term [34, 36, 38].

The "non-gambler" marmosets were able to obtain a considerably higher amount of pellets compared to "gambler" marmosets and to both "gambler" and "non-gambler" rats. This interesting finding is consequent to two independent phenomena: (i) they were able to make the "optimal choice" (i.e., choosing LLL before the indifferent point and SS during the final "gambling" part) and (ii) they progressively increased the number of completed trials, which compensated for the diminished gain associated with SS choice. Such a combination of these two phenomena was never evidenced in "non-gambler" rats during previous studies. Since the marmosets are primates and have well-developed prefrontal cortical areas in comparison with rodents [74], future studies using marmosets would be helpful to analyze neuronal mechanisms underlying the gambling attitude [10].

The results we obtained indicate that the common marmoset can be a suitable model for studies on decision-making under conditions of high uncertainty. A proof of the model validity comes from marmosets' individual reaction to reward-delivery omission. We report a clear-cut dissociation in inadequate responding depending on individual temperament ("gambler" versus "non-gambler"). This seems to resemble what has been reported in the clinical literature: while normal people are likely to modify their own seeking behaviour depending on reward outcome, human pathological gamblers are relatively unaffected by losses, hence persisting in this payoff-seeking activity despite repeated losses [75–78].

Nonhuman primate species differ markedly in their risk preferences: chimpanzees and orangutans are risk-seeking whilst bonobos and lemurs are risk-averse [29, 54, 55]. Although these differences can possibly be explained in terms of feeding ecology, it should be considered that the different risk preferences obtained in nonhuman primate studies are likely due to individual differences (for a review see [17]). Similarly, risk attitude in human behaviour is usually categorized into three types: risk-aversive, risk-prone, and risk-neutral (for a recent review, see [79]). Marked interindividual differences have been already reported in the common marmosets for a number of behavioural domains [80–82]. Furthermore, two recent studies evidenced clear-cut individual differences in decision-making under uncertainty in both rhesus macaques and marmosets ([7, 10]). As for rhesus macaques, it is known that risk sensitivity appears to be partly determined by the serotonergic system: (i) serotonin depletion increases risk proneness [83], a finding consistent with recent rodent data [38]; (ii) a length polymorphism in the gene that codes for serotonin transporter has a role in relation to intraspecific behavioural variability [84]. The aim of future studies will be to further characterize the role played by interindividual variations, by investigating marmosets' genetic profile (with particular reference to polymorphisms in the genes for serotonin receptors and transporter; [85]) and drawing correlations with traits of gambling proneness/aversion.

The setting used in the present study (i.e., operant panels placed inside experimental cages) has the potential to be adapted and used in more extensive ways, for permanent monitoring of subjects' operant-choices and spontaneous (social and nonsocial) behaviour. Such an automated social home-cage system would allow long-term, continuous data collection, which may provide a larger, more accurate picture of gambling-prone behaviour in these species. These systems, in which animals can freely move, interact with each other, and voluntarily access the operant panels, are promising for developing tasks in a more naturalistic environment, with increased ecological validity [17, 86].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

[1] C. Camerer, G. Loewenstein, and D. Prelec, "Neuroeconomics: how neuroscience can inform economics," *Journal of Economic Literature*, vol. 43, no. 1, pp. 9–64, 2005.

[2] A. Rangel, C. Camerer, and P. R. Montague, "A framework for studying the neurobiology of value-based decision making," *Nature Reviews Neuroscience*, vol. 9, no. 7, pp. 545–556, 2008.

[3] M. L. Platt and S. A. Huettel, "Risky business: the neuroeconomics of decision making under uncertainty," *Nature Neuroscience*, vol. 11, no. 4, pp. 398–403, 2008.

[4] C. W. Hill and A. J. Riopelle, "Probability-reward preferences of rhesus monkeys," *The American journal of psychology*, vol. 98, no. 1, pp. 77–84, 1985.

[5] B. Marsh and A. Kacelnik, "Framing effects and risky decisions in starlings," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 5, pp. 3352–3355, 2002.

[6] A. N. McCoy and M. L. Platt, "Risk-sensitive neurons in macaque posterior cingulate cortex," *Nature Neuroscience*, vol. 8, no. 9, pp. 1220–1227, 2005.

[7] B. Y. Hayden and M. L. Platt, "Temporal discounting predicts risk sensitivity in rhesus macaques," *Current Biology*, vol. 17, no. 1, pp. 49–53, 2007.

[8] B. Knutson and P. Bossaerts, "Neural antecedents of financial decisions," *Journal of Neuroscience*, vol. 27, no. 31, pp. 8174–8177, 2007.

[9] K. Doya, "Modulators of decision making," *Nature Neuroscience*, vol. 11, no. 4, pp. 410–416, 2008.

[10] H. Tokuno and I. Tanaka, "Decision making and risk attitude of the common marmoset in a gambling task," *Neuroscience Research*, vol. 71, no. 3, pp. 260–265, 2011.

[11] American Psychiatric Association (A.P.A.), *Diagnostic and Statistical Manual of Mental Disorders*, Washington, DC, USA, 4th edition, 2000.

[12] American Psychiatric Association (A.P.A.), *Diagnostic and Statistical Manual of Mental Disorders*, Washington, DC, USA, 5th edition, 2013.

[13] K. Lowengrub, I. Iancu, A. Aizer, M. Kotler, and P. N. Dannon, "Pharmacotherapy of pathological gambling: review of new treatment modalities," *Expert Review of Neurotherapeutics*, vol. 6, no. 12, pp. 1845–1851, 2006.

[14] L. Bastiani, M. Gori, E. Colasante et al., "Complex factors and behaviors in the gambling population of Italy," *Journal of Gambling Studies*, vol. 29, no. 1, pp. 1–13, 2012.

[15] N. Carragher and L. A. McWilliams, "A latent class analysis of DSM-IV criteria for pathological gambling: results from the National Epidemiologic Survey on Alcohol and Related Conditions," *Psychiatry Research*, vol. 187, no. 1-2, pp. 185–192, 2011.

[16] H. J. Shaffer and D. A. Korn, "Gambling and related mental disorders: a public health analysis," *Annual Review of Public Health*, vol. 23, pp. 171–212, 2002.

[17] F. Paglieri, E. Addessi, F. De Petrillo et al., "Nonhuman gamblers: lessons from rodents, primates, and robots," *Frontiers in Behavioral Neuroscience*, vol. 8, p. 33, 2014.

[18] J. E. Nash, S. H. Fox, B. Henry et al., "Antiparkinsonian actions of ifenprodil in the MPTP-lesioned marmoset model of Parkinson's disease," *Experimental Neurology*, vol. 165, no. 1, pp. 136–142, 2000.

[19] C. Fonta, L. Negyessy, L. Renaud, and P. Barone, "Postnatal development of alkaline phosphatase activity correlates with the maturation of neurotransmission in the cerebral cortex," *Journal of Comparative Neurology*, vol. 486, no. 2, pp. 179–196, 2005.

[20] J. P. Finn and G. H. Lord, "Neurotoxicity studies on sucralose and its hydrolysis products with special reference to histopathologic and ultrastructural changes," *Food and Chemical Toxicology*, vol. 38, no. 2, pp. S7–S17, 2000.

[21] J. R. Foster, "Spontaneous and drug-induced hepatic pathology of the laboratory beagle dog, the cynomolgus macaque and the marmoset," *Toxicologic Pathology*, vol. 33, no. 1, pp. 63–74, 2005.

[22] R. Neubert, M. Foerster, A. C. Nogueira, and H. Helge, "Cross-reactivity of antihuman monoclonal antibodies with cell surface receptors in the common marmoset," *Life Sciences*, vol. 58, no. 4, pp. 317–324, 1995.

[23] A. F. De Vos, D. A. J. Van Riel, M. Van Meurs et al., "Severe T-cell depletion from the PALS leads to altered spleen composition in common marmosets with experimental autoimmune encephalomyelitis (EAE)," *Journal of Neuroimmunology*, vol. 161, no. 1-2, pp. 29–39, 2005.

[24] L. Boon, H. P. M. Brok, J. Bauer et al., "Prevention of experimental autoimmune encephalomyelitis in the common marmoset (*Callithrix jacchus*) using a chimeric antagonist monoclonal antibody against human CD40 is associated with altered B cell responses," *Journal of Immunology*, vol. 167, no. 5, pp. 2942–2949, 2001.

[25] A. Eslamboli, "Marmoset monkey models of Parkinson's disease: which model, when and why?" *Brain Research Bulletin*, vol. 68, no. 3, pp. 140–149, 2005.

[26] C. Geula, N. Nagykery, and C.-K. Wu, "Amyloid-β deposits in the cerebral cortex of the aged common marmoset (*Callithrix jacchus*): incidence and chemical composition," *Acta Neuropathologica*, vol. 103, no. 1, pp. 48–58, 2002.

[27] B. A. 'T Hart, M. Van Meurs, H. P. M. Brok et al., "A new primate model for multiple sclerosis in the common marmoset," *Immunology Today*, vol. 21, no. 6, pp. 290–297, 2000.

[28] A. Vitale, A. Manciocco, and E. Alleva, "The 3R principle and the use of non-human primates in the study of neurodegenerative diseases: the case of Parkinson's disease," *Neuroscience and Biobehavioral Reviews*, vol. 33, no. 1, pp. 33–47, 2009.

[29] E. L. MacLean, T. M. Mandalaywala, and E. M. Brannon, "Variance-sensitive choice in lemurs: constancy trumps quantity," *Animal Cognition*, vol. 15, no. 1, pp. 15–25, 2012.

[30] J. L. Evenden and C. N. Ryan, "The pharmacology of impulsive behaviour in rats: the effects of drugs on response choice with varying delays of reinforcement," *Psychopharmacology*, vol. 128, no. 2, pp. 161–170, 1996.

[31] J. L. Evenden and C. N. Ryan, "The pharmacology of impulsive behaviour in rats VI: the effects of ethanol and selective serotonergic drugs on response choice with varying delays of reinforcement," *Psychopharmacology*, vol. 146, no. 4, pp. 413–421, 1999.

[32] S. Mobini, T.-J. Chiang, M.-Y. Ho, C. M. Bradshaw, and E. Szabadi, "Effects of central 5-hydroxytryptamine depletion on sensitivity to delayed and probabilistic reinforcement," *Psychopharmacology*, vol. 152, no. 4, pp. 390–397, 2000.

[33] S. Mobini, S. Body, M.-Y. Ho et al., "Effects of lesions of the orbitofrontal cortex on sensitivity to delayed and probabilistic reinforcement," *Psychopharmacology*, vol. 160, no. 3, pp. 290–298, 2002.

[34] W. Adriani and G. Laviola, "Delay aversion but preference for large and rare rewards in two choice tasks: implications for the measurement of self-control parameters," *BMC Neuroscience*, vol. 7, article 52, 2006.

[35] W. Adriani, D. Leo, D. Greco et al., "Methylphenidate administration to adolescent rats determines plastic changes on reward-related behavior and striatal gene expression," *Neuropsychopharmacology*, vol. 31, no. 9, pp. 1946–1956, 2006.

[36] W. Adriani, F. Boyer, L. Gioiosa, S. Macrì, J.-L. Dreyer, and G. Laviola, "Increased impulsive behavior and risk proneness following lentivirus-mediated dopamine transporter overexpression in rats' nucleus accumbens," *Neuroscience*, vol. 159, no. 1, pp. 47–58, 2009.

[37] W. Adriani, F. Boyer, D. Leo et al., "Social withdrawal and gambling-like profile after lentiviral manipulation of DAT expression in the rat accumbens," *International Journal of Neuropsychopharmacology*, vol. 13, no. 10, pp. 1329–1342, 2010.

[38] S. Koot, F. Zoratto, T. Cassano et al., "Compromised decision-making and increased gambling proneness following dietary serotonin depletion in rats," *Neuropharmacology*, vol. 62, no. 4, pp. 1640–1650, 2012.

[39] F. Zoratto, G. Laviola, and W. Adriani, "Choice with delayed or uncertain reinforcers in rats: influence of timeout duration and session length," *Synapse*, vol. 66, no. 9, pp. 792–806, 2012.

[40] F. Zoratto, G. Laviola, and W. Adriani, "Gambling proneness in rats during the transition from adolescence to young adulthood: a home-cage method," *Neuropharmacology*, vol. 67, pp. 444–454, 2013.

[41] W. Adriani, S. Koot, L. Saso, R. Van Den Bos, and G. Laviola, "Home cage testing of delay discounting in rats," *Behavior Research Methods*, vol. 41, no. 4, pp. 1169–1176, 2009.

[42] W. Adriani, C. Romani, A. Manciocco, A. Vitale, and G. Laviola, "Individual differences in choice (in)flexibility but not impulsivity in the common marmoset: an automated, operant-behavior choice task," *Behavioural Brain Research*, vol. 256, pp. 554–563, 2013.

[43] T. Sagvolden and J. A. Sergeant, "Attention deficit/hyperactivity disorder—from brain dysfunctions to behaviour," *Behavioural Brain Research*, vol. 94, no. 1, pp. 1–10, 1998.

[44] T. Sagvolden, "Behavioral validation of the spontaneously hypertensive rat (SHR) as an animal model of attention-deficit/hyperactivity disorder (AD/HD)," *Neuroscience and Biobehavioral Reviews*, vol. 24, no. 1, pp. 31–39, 2000.

[45] W. Adriani, A. Caprioli, O. Granstrem, M. Carli, and G. Laviola, "The spontaneously hypertensive-rat as an animal model of ADHD: evidence for impulsive and non-impulsive subpopulations," *Neuroscience and Biobehavioral Reviews*, vol. 27, no. 7, pp. 639–651, 2003.

[46] W. Adriani, F. Zoratto, and G. Laviola, "Brain processes in discounting: consequences of adolescent methylphenidate exposure," in *Behavioral Neuroscience of Attention Deficit Hyperactivity Disorder and Its Treatment, Current Topics in Behavioral Neurosciences*, C. Standford and R. Tannock, Eds., vol. 9, pp. 113–143, Springer, Heidelberg, Germany, 2012.

[47] F. Zoratto, G. Laviola, and W. Adriani, "Delay intolerance task: different impact of timeout duration on impulsive and non-impulsive rats," in *Proceedings of 7th International Conference on Methods and Techniques in Behavioral Research*, pp. 422–424, Eindhoven, The Netherlands, 2010.

[48] T. R. Zentall and J. R. Laude, "Do pigeons gamble? I wouldn't bet against it," *Current Directions in Psychological Science*, vol. 22, no. 4, pp. 271–277, 2013.

[49] K. F. Pattison, J. R. Laude, and T. R. Zentall, "Environmental enrichment affects suboptimal, risky, gambling-like choice by pigeons," *Animal Cognition*, vol. 16, no. 3, pp. 429–434, 2013.

[50] T. R. Zentall, "Maladaptive "gambling" by Pigeons," *Behavioural Processes*, vol. 87, no. 1, pp. 50–56, 2011.

[51] T. R. Zentall and J. Stagner, "Maladaptive choice behaviour by pigeons: an animal analogue and possible mechanism for gambling (sub-optimal human decision-making behaviour)," *Proceedings of the Royal Society B-Biological Sciences*, vol. 278, no. 1709, pp. 1203–1208, 2011.

[52] M. K. Chen, V. Lakshminarayanan, and L. R. Santos, "How basic are behavioral biases? Evidence from capuchin monkey trading behavior," *Journal of Political Economy*, vol. 114, no. 3, pp. 517–537, 2006.

[53] V. R. Lakshminarayanan, M. K. Chen, and L. R. Santos, "The evolution of decision-making under risk: framing effects in monkey risk preferences," *Journal of Experimental Social Psychology*, vol. 47, no. 3, pp. 689–693, 2011.

[54] D. B. M. Haun, C. Nawroth, and J. Call, "Great Apes' risk-taking strategies in a decision making task," *PLoS ONE*, vol. 6, no. 12, Article ID e28801, 2011.

[55] S. R. Heilbronner, A. G. Rosati, J. R. Stevens, B. Hare, and M. D. Hauser, "A fruit in the hand or two in the bush? Divergent risk preferences in chimpanzees and bonobos," *Biology Letters*, vol. 4, no. 3, pp. 246–249, 2008.

[56] A. Ibáñez, C. Blanco, I. Perez De Castro, J. Fernandez-Piqueras, and J. Sáiz-Ruiz, "Genetics of pathological gambling," *Journal of Gambling Studies*, vol. 19, no. 1, pp. 11–22, 2003.

[57] D. C. De Comings, R. Gade-Andavolu, N. Gonzalez et al., "The additive effect of neurotransmitter genes in pathological gambling," *Clinical Genetics*, vol. 60, no. 2, pp. 107–116, 2001.

[58] J. Reuter, T. Raedler, M. Rose, I. Hand, J. Gläscher, and C. Büchel, "Pathological gambling is linked to reduced activation of the mesolimbic reward system," *Nature Neuroscience*, vol. 8, no. 2, pp. 147–148, 2005.

[59] M. A. Donati, F. Chiesi, and C. Primi, "A model to explain at risk/problem gambling among male and female adolescents: gender similarities and differences," *Journal of Adolescence*, vol. 36, no. 1, pp. 129–137, 2013.

[60] M. N. Potenza, "Neurobiology of gambling behaviours," *Current Opinion in Neurobiology*, vol. 23, no. 4, pp. 660–667, 2013.

[61] T. Toneatto, T. Blitz-Miller, K. Calderwood, R. Dragonetti, and A. Tsanos, "Cognitive distortions in heavy gambling," *Journal of Gambling Studies*, vol. 13, no. 3, pp. 253–266, 1997.

[62] R. Ladouceur, A. Gaboury, M. Dumont, and P. Rochette, "Gambling: relationship between the frequency of wins and irrational thinking," *The Journal of Psychology: Interdisciplinary and Applied*, vol. 122, no. 4, pp. 409–414, 1988.

[63] J. Joukhador, F. Maccallum, and A. Blaszczynski, "Differences in cognitive distortions between problem and social gamblers," *Psychological Reports*, vol. 92, no. 3, pp. 1203–1214, 2003.

[64] R. L. Reid, "The psychology of the near miss," *Journal of Gambling Behavior*, vol. 2, no. 1, pp. 32–39, 1986.

[65] M. Griffiths, "Psychobiology of the near-miss in fruit machine gambling," *The Journal of psychology*, vol. 125, no. 3, pp. 347–357, 1991.

[66] L. Clark, "Decision-making during gambling: an integration of cognitive and psychobiological approaches," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 365, no. 1538, pp. 319–330, 2010.

[67] C. A. Winstanley, P. J. Cocker, and R. D. Rogers, "Dopamine modulates reward expectancy during performance of a slot machine task in rats: evidence for a near-miss effect," *Neuropsychopharmacology*, vol. 36, no. 5, pp. 913–925, 2011.

[68] M. J. Frank, L. C. Seeberger, and R. C. O'Reilly, "By carrot or by stick: cognitive reinforcement learning in Parkinsonism," *Science*, vol. 306, no. 5703, pp. 1940–1943, 2004.

[69] R. Cilia, J. H. Ko, S. S. Cho et al., "Reduced dopamine transporter density in the ventral striatum of patients with Parkinson's disease and pathological gambling," *Neurobiology of Disease*, vol. 39, no. 1, pp. 98–104, 2010.

[70] M. Pettorruso, G. Martinotti, A. Fasano et al., "Anhedonia in Parkinson's disease patients with and without pathological gambling: a case-control study," *Psychiatry Research*, vol. 215, no. 2, pp. 448–452, 2014.

[71] J. W. Young, J. Van Enkhuizen, C. A. Winstanley, and M. A. Geyer, "Increased risk-taking behavior in dopamine transporter knockdown mice: further support for a mouse model of mania," *Journal of Psychopharmacology*, vol. 25, no. 7, pp. 934–943, 2011.

[72] S. Roberts and A. Gharib, "Variation of bar-press duration: where do new responses come from?" *Behavioural Processes*, vol. 72, no. 3, pp. 215–223, 2006.

[73] C. W. Schindler, L. V. Panlilio, and S. R. Goldberg, "Second-order schedules of drug self-administration in animals," *Psychopharmacology*, vol. 163, no. 3-4, pp. 327–344, 2002.

[74] G. Paxinos, C. Watson, M. Petrides, M. Rosa, and H. Tokuno, *The Marmoset Brain in Stereotaxic Coordinates*, Academic Press, San Diego, Calif, USA, 2011.

[75] A. E. Goudriaan, J. Oosterlaan, E. De Beurs, and W. Van Den Brink, "Pathological gambling: a comprehensive review of biobehavioral findings," *Neuroscience and Biobehavioral Reviews*, vol. 28, no. 2, pp. 123–141, 2004.

[76] R. J. van Holst, W. van den Brink, D. J. Veltman, and A. E. Goudriaan, "Why gamblers fail to win: a review of cognitive and neuroimaging findings in pathological gambling," *Neuroscience and Biobehavioral Reviews*, vol. 34, no. 1, pp. 87–107, 2010.

[77] R. J. van Holst, J. N. van der Meer, D. G. McLaren, W. van den Brink, D. J. Veltman, and A. E. Goudriaan, "Interactions between affective and cognitive processing systems in problematic gamblers, a functional connectivity study," *PLoS ONE*, vol. 7, no. 11, Article ID e49923, 2012.

[78] R. J. Van Holst, D. J. Veltman, C. Bchel, W. Van Den Brink, and A. E. Goudriaan, "Distorted expectancy coding in problem gambling: is the addictive in the anticipation?" *Biological Psychiatry*, vol. 71, no. 8, pp. 741–748, 2012.

[79] J. B. Engelmann and D. Tamir, "Individual differences in risk preference predict neural responses during financial decision-making," *Brain Research*, vol. 1290, pp. 28–51, 2009.

[80] B. Reynolds, A. Ortengren, J. B. Richards, and H. de Wit, "Dimensions of impulsive behavior: personality and behavioral measures," *Personality and Individual Differences*, vol. 40, no. 2, pp. 305–315, 2006.

[81] C. F. Chabris, D. Laibson, C. L. Morris, J. P. Schuldt, and D. Taubinsky, "Individual laboratory-measured discount rates predict field behavior," *Journal of Risk and Uncertainty*, vol. 37, no. 2-3, pp. 237–269, 2008.

[82] N. A. Shamosh, C. G. DeYoung, A. E. Green et al., "Individual differences in delay discounting: relation to intelligence, working memory, and anterior prefrontal cortex," *Psychological Science*, vol. 19, no. 9, pp. 904–911, 2008.

[83] A. B. Long, C. M. Kuhn, and M. L. Platt, "Serotonin shapes risky decision making in monkeys," *Social Cognitive and Affective Neuroscience*, vol. 4, no. 4, Article ID nsp020, pp. 346–356, 2009.

[84] K. K. Watson, J. H. Ghodasra, and M. L. Platt, "Serotonin transporter genotype modulates social reward and punishment in rhesus macaques," *PLoS ONE*, vol. 4, no. 1, 2009.

[85] A. M. Santangelo, M. Ito, O. 'Dea L, H. F. Clarke, A. Ferguson-Smith, and A. C. Roberts, "Novel serotonin transporter polymorphism in the common marmoset (*Callithrix jacchus*) contributes to anxious behaviour," *Journal of Psychopharmacology*, vol. 25, no. 8, p. A73, 2011.

[86] R. van den Bos, W. Davies, F. Dellu-Hagedorn et al., "Cross-species approaches to pathological gambling: a review targeting sex differences, adolescent vulnerability and ecological validity of research tools," *Neuroscience and Biobehavioral Reviews*, vol. 37, part 2, no. 10, pp. 2454–2471, 2013.