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EDITORIAL

Evidence for using pimavanserin for the treatment of Parkinson's disease psychosis

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Abstract

The aim of this editorial is to evaluate the evidence for using pimavanserin for the treatment of Parkinson's disease psychosis (PDP) from randomized controlled trials (RCTs). We only identified two published trials that evaluated the use of pimavanserin among individuals with PDP. Both studies found that pimavanserin improved psychotic symptoms among individuals with PDP when compared to placebo. Pimavanserin was fairly well tolerated in both studies and did not appear to cause significant sedation or worsen motor symptoms among individuals with PDP. However, given the limited data, additional confirmatory studies are required before pimavanserin can be considered as a first line agent for the treatment of psychotic symptoms among individuals with PD.

Key words: Pimavanserin; Parkinson's disease; Parkinson's disease psychosis; Psychosis; Antipsychotic

Core tip: Pimavanserin is an atypical antipsychotic that was the first medication to be

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approved by the Food and Drug Administration for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP). There are only two published trials that have evaluated the use of pimavanserin among individuals with PDP. Both studies are of good quality and found that pimavanserin improves psychotic symptoms among individuals with PDP when compared to placebo. Additionally, pimavanserin was fairly well tolerated in both studies and did not appear to cause significant sedation or worsen motor symptoms among individuals with PDP.

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INTRODUCTION

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that presents with tremors, bradykinesia, rigidity and postural instability[1]. After Alzheimer's disease (AD), PD is the second-most common neurodegenerative disorder in the United States[2]. Approximately 630000 individuals in the United States have a diagnosis of PD, with the diagnosed prevalence of PD likely to double by 2040. The prevalence for PD increases with age ranging from approximately 41 per 100000 people of 40 to 49 years of age to 1903 per 100000 population in individuals ≥ 80 years of age[3]. The economic burden of PD is reflected by the incurred medical expenses approximating $14 billion in 2010 which was $8.1 billion higher than expected for a similar population without PD[2].

Psychotic symptoms are not uncommon among individuals with PD with a prevalence rate of approximately 25%-30%[4,5]. The National Institute of Neurological Disorders and Stroke and National Institute of Mental Health combined work group used the term "PD psychosis" (PDP) to describe the various psychotic symptoms that present as a continuum of PD progression rather than representing a distinct symptom class[6]. For the diagnosis of PD psychosis to made, the following criteria should be met: (1) The presence of at least one of the following symptoms: illusions, false sense of presence, hallucinations or delusions; (2) A primary diagnosis of PD; (3) Meet the United Kingdom brain bank criteria for PD; (4) The psychotic symptoms occurred after the diagnosis of PD was made; (5) The symptom(s) are recurrent or continuous for 1 mo; (6) The symptoms are not better accounted for by another cause of Parkinsonism such as dementia with Lewy bodies, psychiatric disorders such as schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features, or a general medical condition including delirium; and (7) These symptoms could be associated with or without insight, with or without dementia, and with or without treatment for PD.

Risk factors for PDP include the presence of dementia, older age, reduced vision, longer duration of illness, high severity of illness, presence of depression, sleep disturbance and REM behavior disorder, axial rigidity subtype of PD, and exposure to dopamine agonists (DA)[7,8]. The presence of PDP is associated with greater caregiver stress, poorer quality of life for the individual with PD, higher rates of institutionalization or nursing home placement, and increased mortality[8]. A recent analysis of all health resource utilization (HRU) and total costs found that mean 12-mo HRU per patient was 2.3 times higher and costs were 2.1 times higher in the PDP cases, while falls were 3.4 times higher and fractures 2.3 times higher respectively[9].

The pathogenesis of PDP is yet to be clearly understood but present data indicates significant dysfunction in attention, executive functions, and visuospatial functions in these individuals[10]. Additionally, neuroimaging studies reveal grey matter atrophy in regions of the brain corresponding to dorsal and ventral visual pathways, the hippocampus, and cholinergic structures. Furthermore, functional imaging studies suggest the existence of an aberrant top-to-bottom visual processing system which dominates the normal bottom-to-top system in individuals with PD and visual hallucinations. Nucleotide polymorphisms of several genes have been studied among individuals with PDP, but thus far the 45C>T polymorphisms of the cholecystokinin gene (*CCK*) appears to have had the most potential in elucidating pathological pathways of PDP[10].

PDP may also occur partially due to medications that are used to the treat motor symptoms of PD[11]. Hence, a part of treating PDP also involves the reduction or discontinuation of anticholinergic medications, monoamine oxidase inhibitors, levodopa, or DA which may be worsening or causing symptoms of PDP[12,13]. If medication adjustments are not appropriate or they do not resolve the PDP symptoms, then available data from controlled trials indicate there is some benefits for use of antipsychotic medications, the acetylcholinesterase inhibitor-rivastigmine, and NMDA antagonist-memantine for treating PDP[4]. Uncontrolled trials also indicate some benefit for low-dose apomorphine[4,14-17] and electroconvulsive therapy (ECT)[18-20] for treating PDP. However, none these therapies are approved by the United States Food and Drug Administration (FDA) for the treatment of PDP.

A recent systematic review by Wilby *et al*[21] that assessed the treatment for PDP included data from 16 studies. Eleven of these studies compared active drugs to placebo whereas 5 studies compared clozapine to another active drug. The placebo-controlled trials demonstrated benefit for clozapine and pimavanserin (Nuplazid) for the treatment of PDP with no definitive benefits noted for either quetiapine or olanzapine. The comparative studies demonstrated improvements in PDP symptoms when clozapine or comparator drug were assessed alone. However, the data did not suggest any superiority of one active drug over the other drugs.

Pimavanserin is an atypical antipsychotic medication and is now the first medication to be approved by the FDA for the treatment of hallucinations and delusions associated with PDP[22]. Pimavanserin is a selective 5-HT2A inverse agonist that has low affinity for 5-HT2C and sigma-1 receptors. Additionally, pimavanserin lacks activity at dopaminergic, muscarinic, adrenergic, and histaminergic receptors. Pimavanserin is mainly metabolized in the liver through the cytochrome P450 system (CYP3A4 and CYP3A5) and is excreted primarily through the urine. Approximately 95% of pimavanserin is protein bound. Pimavanserin has a mean peak onset in 6 h with a half-life of 55 to 60 h.

EVIDENCE FOR USING PIMAVANSERIN FOR THE TREATMENT OF PARKINSON'S DISEASE PSYCHOSIS

We identified and reviewed a total of two randomized controlled trials (RCTs) that evaluated the use of pimavanserin among individuals with PDP[23,24]. Both studies were rated as being of good quality based on the center for evidence-based medicine criteria[25] (Table 1). We discuss both studies in depth below, while a brief summary of both studies is outlined in Table 2.

Meltzer et al[23] study

The study by Meltzer *et al*[23] was a phase 2 multicenter, randomized, placebo-controlled, double-blind trial that compared pimavanserin to placebo among individuals with PDP. The trial was 4 wk in duration with a 4-wk follow-up period. The participants received pimavanserin or placebo in a 1:1 ratio, after completion of screening and baseline evaluations. The dosing of the study drug was 20 mg on day 1 with possible increases to 40 mg a day and 60 mg a day on study days 8 and 15, depending on the participants' response to the medication. The staging of PD was done at baseline using the modified Hoehn and Yahr Unified Parkinson's Disease Rating Scale (UPDRS Part V). The psychotic symptoms were evaluated using the Scale for the Assessment of Positive Symptoms (SAPS), the Parkinson's Psychosis Rating Scale (PPRS) and the Clinical Global Impression-Severity (CGI-S) scale. The effect of treatment on mentation, behavior, mood, complications of therapy and activities of daily living were assessed using the UPDRS Parts I, IV and VI. Daytime sleepiness was evaluated using the Epworth Sleepiness Scale. The motor symptoms were assessed using the UPDRS Parts II (Activities in Daily Living) and III (Motor Examination) respectively. An adverse event check list, vital signs, laboratory tests, physical examinations and electrocardiograms (ECG) were also completed.

The participants were assessed at screening/baseline (up to 14 d prior to study day 1). The study visits were days 1, 8, 15, 28, and 57. Visit day 57 was a safety data evaluation visit. The investigators completed a physical examination, vital signs and laboratory tests at each study visit. From day 1 to 57, the adverse events were noted and assigned severity and relationship to treatment.

The investigators noted improvements in the global rating of hallucination (P = 0.02, effect size 0.71), persecutory delusions domain score (P = 0.009, effect size 0.69) and in the ideas and delusions of reference domain score (P = 0.05, effect size 0.56) in the pimavanserin group when compared to the placebo group. Additionally, improvements were noted in the global rating of delusions (P = 0.03, effect size 0.58)

Table 1 Quality of studies reviewed

Name of publication of study	Yr	Random-ization?	Similar groups initially?	Equal treatments?	All participants accounted for?	Analyzed in groups to which they were randomized?	Objective/"bli-nd" treatments?	Overall quality of the study
Meltzer *et al*[23]	2010	Yes	Yes	Yes	Yes	Yes	Yes	Good
Cummings *et al*[24]	2014	Yes	Yes	Yes	Yes	Yes	Yes	Good

and the sum of global ratings total (hallucinations and delusions) scores (P = 0.02, effect size 0.66) in the pimavanserin group when compared to the placebo group. Furthermore, a trend was noted in improvement in the sum of total (hallucinations and delusions) domain scores (P = 0.09, effect size 0.56) in the pimavanserin group when compared to the placebo group. The investigators also noted improvements in the UPDRS Part I total score (P = 0.05, effect size 0.43) in the pimavanserin group when compared to the placebo group. Improvements were also noted in the UPDRS IV (complications of therapy) scores (P = 0.06, effect size 0.55) in the pimavanserin group when compared to placebo but did not reach statistical significance. However, there were no significant improvements noted in the UPDRS Part II and III (P = 0.83, 0.40, 0.74 respectively), the PPRS scores (P = 0.11, effect size 0.48), the CGI-S (P = 0.20, effect size 0.58) and the UPDRS VI (activities of daily living) scores (P = 0.22, effect size 0.41) in the pimavanserin group when compared to placebo group.

The investigators did not identify any significant differences between the pimavanserin and placebo groups on the treatment-emergent adverse events (72.4% *vs* 77.4%). The most common adverse effects noted in the pimavanserin group were somnolence, edema and increase in blood urea nitrogen (all 10.3%). They noted that balance disorder and freezing phenomenon occurred in 6.9% of pimavanserin treated individuals when compared to none of the placebo treated individuals. Additionally, "on and off" phenomenon was noted in 3.4% of pimavanserin treated individuals when compared to none of the placebo treated individuals.

There are multiple weaknesses in in this study to be highlighted. The study had a small sample size; only 44 total subjects (20 in pimavanzserin group and 24 in placebo group) completed the study. There was also noted to be a relatively high attrition rate in the pimavanserin group (n = 9 or 31%) compared to placebo group (n = 7 or 23%) with the most common reason they dropped out being described as "other reasons". The dropout rate was greater than the estimated 10% dropout rate the authors predicted in their analysis, although they report that ITT and PP analysis results were similar. It is also noteworthy that in the study design utilized relatively rapid dose escalation. Pimavanserin takes 10-14 d to reach steady state. Thus, escalating the dose after 1 wk of treatment may have led to insufficient time to achieve full efficacy. The study also did not assess the time of onset of delusions or hallucinations in relation to the duration of treatment with L-DOPA, which leaves a potential confounding factor. An additional confounding factor to consider is that they also did not assess the efficacy of primavanserin in patients who were not receiving dopaminomimetic drugs. Also since the study is just placebo controlled, there is no comparison of efficacy/tolerability between pimavenserin and other antipsychotics such as clozapine.

Cummings et al[24] study

The study by Cummings *et al*[24] study was a randomized, double-blind, parallel group, placebo-controlled trial that enrolled participants with PDP from 52 centers (academic hospitals or neurology research centers) in the United States and two centers in Canada. The eligible participants were randomized to receive either pimavanserin (40 mg daily) or matched placebo in a 1:1 ratio in a double-blind manner. The assessments were completed at baseline and days 15, 29 and 43. The primary outcome was the change in total Parkinson's disease-adapted scale for assessment of positive symptoms (SAPS-PD) score from baseline to day 43. The secondary outcomes were the change by day 43 in CGI-S and improvement (CGI-I) scale scores. The other measures were the Zarit 22-item care giver burden scale, scales for outcomes in PD-sleep (parts B and C) assessing night-time sleep quality (SCOPA-NS) and daytime wakefulness (SCOPA-DS) and the UPDRS II and III. Safety was assessed by evaluating the use of concomitant drug use, adverse events, physical examination, clinical laboratory tests, vital signs and ECG.

Table 2 Summary of studies

Name of study	Yr	Country of origin	Total number of participants	Age	Type of setting	Comparators	Duration
Meltzer *et al*[23]	2010	United States	60	Mean age 70.9 yr	Unclear	Pimavanserin *vs* placebo	4 wk
Cummings *et al*[24]	2014	United States and Canada	199	Mean age 72.4 yr	Academic hospitals and neurology research centers	Pimavanserin *vs* placebo	6 wk

The investigators noted improvements in the total SAPS-PD score (P = 0.0014, effect size 0.50), the CGI-I score (P = 0.0012, effect size 0.50) and the CGI-S score (P = 0.0007, effect size 0.52) in the pimavanserin group when compared to placebo group. Additionally, improvements were noted in the SCOPA-night score (P = 0.04, effect size 0.31) and the SCOPA-day wake score (P = 0.01, effect size 0.39) in the pimavanserin group when compared to placebo group. Furthermore, improvements were noted in the Zarit Caregiver burden score (P = 0.0016, effect size 0.50) in the pimavanserin group when compared to placebo group. The investigators also noted non-significant improvements in both pimavanserin and placebo groups (-1.69 and -1.40) in the motor function (UPRDRS II and III) composite score.

The investigators did not find any treatment related impairment of motor functioning in the pimavanserin or placebo group. 10% of the participants in the pimavanserin group discontinued the study due to adverse events when compared to 2% of the participants in the placebo group. They did not identify any significant difference between the pimavanserin and placebo groups on the occurrence of treatment emergent adverse events. A total of 11% of participants in the pimavanserin group and 4% of the individuals in the placebo group had serious adverse events. There was a 7.3 ms increase in the QTc interval on day 43 in the pimavanserin group when compared to none in the placebo group.

There are some weaknesses to consider with this study. The study does not provide sufficient safety data or evidence about durability of response beyond 6 wk. The duration of the trial also limits the ability to look at long term benefits such as reduced nursing home admission and caregiver burden. A confounding factor to consider is that 99% of subjects in both placebo and pimavanserin group were using dopaminergic medications at baseline and throughout the RCT indicating they were not able to study efficacy of pimavanserin in patients not on dopaminergic drugs. Additionally, as with the Meltzer *et al*[23] study there is no comparison of efficacy/tolerability between pimavenserin and other antipsychotics such as clozapine.

DISCUSSION

Data available from these two well-designed studies indicates that pimavanserin improves psychotic symptoms (delusions and hallucinations) among individuals with PDP when compared to placebo[23,24]. Additionally, pimavanserin appears to be fairly well tolerated with no worsening of the motor symptoms of PD. Furthermore, no increase in mortality rates was noted among pimavanserin treated individuals in both studies.

A meta-analysis by Yasue *et al*[26] that included data from 4 RCTs that studied the use of pimavanserin for PDP. This meta-analysis included 417 pimavanserin-treated and 263 placebo-treated individuals with PDP. The investigators found that pimavanserin decreased the symptoms of hallucinations and delusions when compared to placebo [weighted mean differences (WMD) = –2.26, P = 0.005]. In addition, pimavanserin was found to be superior to placebo when evaluating the reduction in the symptoms of hallucinations (WMD = –2.15, P = 0.001) and delusions (WMD = –1.32, P = 0.010) independently. The investigators did not find any significant difference between pimavanserin and placebo on the all-cause discontinuation rates for adverse events, death, Parkinson motor symptoms and the incidence of individual adverse events. Pimavanserin was also associated with less orthostatic hypotension when compared to placebo (risk ratio = 0.33, P = 0.008, number needed to harm = 17, P = 0.01). The investigators concluded that pimavanserin is beneficial for the treatment of symptoms of PDP and is well tolerated.

In addition to the data from the two studies that we found from our literature search, Yasue *et al*[26] included data from two unpublished studies of pimavanserin

among individuals with PDP in their meta-analysis[27,28]. Both the studies were multicenter trials that were of 6 wk in duration. The average age of the participants among the two studies was 69.3 and 72 years respectively. The first study had 295 participants and the second study had 121 participants. The first study compared pimavanserin 10 mg a day and 40 mg a day to placebo, and the second study compared pimavanserin 10 mg a day and 20 mg a day to placebo. Although pimavanserin was well tolerated in these studies, pimavanserin did not appear to significantly improve psychotic symptoms among individuals with PDP when compared to placebo. Pimavanserin appeared to be well tolerated in these studies with no difference noted between pimavanserin and placebo groups in terms of discontinuation rates for any cause, adverse effects, serious adverse effects and deaths.

A summary of the United States FDA's review of the safety and effectiveness for pimavanserin for PDP included a total of 616 individuals who received at least 1 dose of pimavanserin, with a total exposure of 825 patient-years in the PDP population[29]. The FDA found that pimavanserin 34 mg a day was effective in treating hallucinations and delusions among individuals with PDP. Available data indicated that 80.5% of individuals treated with pimavanserin experienced at least some improvement in symptoms when compared to 58.1% of placebo treated individuals. Pimavanserin did not appear to worsen motor functioning among individuals with PDP. The authors concluded that pimavanserin is the only FDA-approved treatment for the hallucinations and delusions among individuals with PDP. Despite pimavanserin's different pharmacologic mechanism when compared to other atypical antipsychotics, the FDA remains concerned about the increased risk of death seen with other antipsychotic use among older adults. Thus Pimavanserin was also given the same boxed warning regarding the risk of death associated with antipsychotic use among older adults with dementia.

Pimavanserin's package insert indicates that the drug prolongs QT interval and its use should be avoided among individuals with known QT prolongation or in combination with other drugs that can prolong the QT interval including antiarrhythmics (quinidine, procainamide, amiodarone), certain anti-psychotic medications (ziprasidone, chlorpromazine, thioridazine) and certain antibiotics (gatifloxacin, moxifloxacin)[30]. Additionally, pimavanserin should be avoided among individuals with a history of cardiac arrhythmias, in situations that may increase the risk of torsades de pointes and/or sudden death including symptomatic bradycardia, hypokalemia or hypomagnesemia, and in the presence of congenital prolongation of the QT interval. However our review of the literature did not find any evidence of clinically significant increase in QTc with the use of pimavanserin among individuals with PDP. This data is consistent with the data from the Yasue *et al*[26] meta-analysis.

A recent 6-wk randomized, placebo-controlled, double-blind study that included 181 participants who lived in nursing homes and had possible or probable AD and psychotic symptoms found that pimavanserin improved psychotic symptoms among these individuals at 6 wk when compared to placebo (Cohen's d = -0.32; P = 0.045)[31]. However, by week 12 the investigators found no significant advantage for pimavanserin when compared to placebo (P = 0.561). Common adverse events noted in the study when comparing pimavanserin *vs* placebo were falls (23% *vs* 23%), urinary tract infections (22% *vs* 28%) and agitation (21% *vs* 14%). Treatment discontinuation due to adverse events was seen in 9% of pimavanserin treated individuals when compared to 12% of the placebo treated individuals. There was no significant difference between the pimavanserin and placebo treated individuals on cognition or motor functioning.

A Pennsylvania-based non-profit organization published reports of post-marketing adverse events include hallucinations, confused states and deaths with the use of pimavanserin[32]. The data published by Institute for Safe Medication Practices in November 2017 indicates that in total there were 2236 adverse events for the 12 mo post-marketing observation period ending in March 2017[33]. The four most frequently reported adverse events were hallucinations 487 (21.8%) drug ineffectiveness 333 (14.9%), confused state 258 (11.5%) and death 244 (10.9%).

The United States FDA completed a review of all post-marketing reports of deaths and serious adverse events reported with the use of pimavanserin[34]. The FDA did not identify any new or unexpected safety findings with pimavanserin or findings that were inconsistent with the established safety profile currently described for the drug. The FDA concluded that the drug's benefits outweigh its risks for patients with hallucinations and delusions of PDP.

CONCLUSION

Data available from two well-designed studies indicates that pimavanserin improves psychotic symptoms among individuals with PD when compared to placebo. In addition, pimavanserin appears to be fairly well tolerated with no serious adverse effects and it does not appear to worsen the motor symptoms of PD. Additional well controlled studies with positive data for both efficacy and safety are required before pimavanserinin can be designated as the first line agent for use among individuals with PDP.

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ORIGINAL ARTICLE

Observational Study

Problematic Internet use in drug addicts under treatment in public rehab centers

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Abstract

BACKGROUND

Problematic Internet use (PIU) or Internet addiction has been recognized to be a behavioral addiction characterized by excessive or poorly controlled preoccupations, urges, or behaviors regarding computer use and Internet access that leads to impairment or distress resembling substance abuse.

AIM

To investigate the prevalence and characteristics of Internet use and abuse in a group of drug addicts from Southern Italy, by means of a specific questionnaire ["Questionario sull'Utilizzo delle Nuove Tecnologie" (QUNT)].

METHODS

All subjects (183) were heavy smokers, almost 50% of them used heroin and/or opioid compounds, 30% alcohol, 10% cannabis, 8% cocaine, and 5% were polydrug users. Almost 10% of the individuals were also suffering from gambling disorder.

RESULTS

The time spent online was more than 4 hours a day in the total sample, with a slight prevalence in male subjects. Cocaine and cannabis users spent more than 6 hours online, significantly more than opioid and alcohol abusers. Distribution of the QUNT factors was not different in both sexes. Cocaine users showed higher scores at the "loss of control", "pornography addiction", and "addiction to social networks" factors, for the stimulant effect of this substance. Moreover, 15 out of the total 17 cocaine users were pathological gamblers. Positive and statistically significant relationships were observed between some QUNT factors and body mass index.

CONCLUSION

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These findings indicate that PIU is less severe in subjects taking sedative substances, such as heroin/opioids and alcohol, than in subjects taking stimulants. Alternatively, it may be used as a "stimulant" trigger in cocaine and cannabis users. Flattening effect of abuse drugs was noted on possible sex-related differences in QUNT items. We observed a sort of "protective" effect of a love relationship and/or living together with a partner, as those engaged subjects showed lower scores on different items than single subjects or those living alone. The relationship between time spent online (and related sedentary lifestyle) and body mass index would suggest that Internet use might be a contributing factor to increasing weight gain and obesity amongst adolescents and young adults worldwide. Our findings also highlighted the specific vulnerability of drug addicts who use stimulants, rather than sedative compounds, to other kinds of behavioral addictions, such as gambling disorder.

Key words: Internet; Problematic Internet use; Behavioral addictions; Drug abuse; Rehab centers

Core tip: This study investigated the characteristics of Internet use and problematic Internet use (PIU) in drug addicts through a specific questionnaire. The findings indicated that PIU is more common in subjects taking cocaine and cannabis than in subjects taking opioids or alcohol, and that the also affected by pathological gambling disorder. This suggests a favoring role of stimulant drugs towards the development of behavioral addictions. The relationship between time spent online and body mass index indicates that Internet use might be a factor that promotes weight gain and obesity. Addiction prevention should take into consideration PIU, which currently represents a worldwide epidemic.

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INTRODUCTION

New technologies, when used appropriately, undoubtedly constitute a resource that can greatly improve the quality of an individual's life. The Internet is probably one of the biggest revolutions of the last few years because it has transformed the way of communicating, exchanging information, participating in real-time events thousands of kilometers away, and finding easily and rapidly any kind of information[1,2]. In the same way, it should be noted that the mismatched use of the Internet constitutes, especially where predisposing psychopathological factors are present, a real risk for a subject's mental health, as it may become a problem out of his/her control.

In particular, the abuse of the Internet represents the most dangerous and probable threat that may cause serious impairment to the social, psychological, working, and emotional individual adjustments. Over the last 15 years, the number of Internet users has increased by 1000%[3] , as documented by the Internet World Stats, Pigdom, a society that features up to date world Internet usage, population statistics, and other issues[3]. Not surprisingly, as a result, studies on abuse of the Internet have proliferated. This problem is not yet well understood, and research on its etiology is still at its beginning[4].

Problematic Internet use (PIU) or Internet addiction is a behavioral addiction[5] that can be defined as "use of the Internet that creates psychological, social, school, and/or work difficulties in a person's life"[6].

Increasing literature on PIU led the American Psychiatric Association to include Internet Gaming Disorder in section 3 of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5), but the current opinion is that more data are needed before incorporating it in the manual as a condition with a nosological dignity[7-9]. In 2008, Block[7] suggested four diagnostic criteria essential to a possible diagnosis of PIU

as an addictive behavior, as follows: "Excessive Internet use associated with a loss of sense of time; withdrawal, including feelings of anger, depression and tension when Internet is not accessible; tolerance, including the need for better computer equipment, more software, or more hours of use, and adverse consequences, including arguments, lying, poor school/work or vocational achievement, social isolation, and fatigue"[7].

Generally, PIU subjects are not aware that they have a problem[10-12] that may progressively impair family, school, work, or social life[13] or lead to severe social withdrawal[12,14] and even suicide[12,15-17]. Several studies have documented the negative consequences of PIU, but the literature does not reflect a consistent conceptualization of this behavior[18,19]. Specifically, it is unclear whether PIU should be classified as a type of behavioral addiction[19], an impulse control disorder, a subtype of obsessive-compulsive disorder[20-24], or an impaired way of coping with stress[25-27].

The most common symptoms of PIU are similar to those of substance use disorders (SUDs) according to DSM-5[28] including unpredictable behavior and mood[14,15], craving, excessive concerns about Internet activities, and inability to reduce its use[29,30]. Some researchers made some parallelisms with behavioral addictions, including gambling disorder[22,31]. Again, neurobiological studies indicate that PIU shares with SUDs several neurobiological characteristics[15,32-34]. Although PIU has been found frequently comorbid with other psychiatric disorders[35], the literature on the relationship between PIU and SUDs is meager.

The same is true for data on PIU prevalence and characteristics in our country. Therefore, the present study aimed at exploring these phenomena in a peculiar population constituted by individuals following a rehab program for drug addictions in public centers (Servizio Tossicodipendenze, SERT) through a questionnaire called "Questionario sull'Utilizzo delle Nuove Tecnologie" (QUNT) that we had created for this purpose.

MATERIALS AND METHODS

Self-assessment questionnaire

A specific interactive platform and website (http://dronet.araneus.it/questionario) on new technologies were created on an external server. The platform allowed access to the self-assessment questionnaire only *via* the Internet.

At the same time, a self-assessment questionnaire referred to the acronym QUNT was developed. The QUNT consists of two sections, one for demographic data and another consisting of 101 items (Appendix 1). Forty-five out of the total 101 items had five possible answers, according to a Likert five-point scale with 1 indicating "completely false" and 5 indicating "completely true"; three items were multiple-choice questions; ten were focused on the use of "instant messaging" (with five possible answers, according to a Likert five-point scale with 1 indicating "completely false" and 5 indicating "completely true"), and 42 items on the use of "social networks" (instant messaging: Whatsapp, Telegram, Skype, and social networks: Facebook, Twitter and Instagram) (with five possible answers, according to a Likert five-point scale with 1 indicating "completely false" and 5 indicating "completely true"). The item #101 was actually a question on the satisfaction/utility or not with the questionnaire. The items considered of greater relevance were put together in order to identify factors built according to *a priori* criteria extrapolated from the data available in the scientific literature[6,26,29]. These factors were "time spent online" (item 2, 3, 4, 5, 6, 7, 25, 33), "social withdrawal" (item 8, 10, 18, 22, 30, 35), "abstraction from reality" (item 11, 13, 24), "loss of control" (item 19, 20, 32, 36), "addiction to pornography" (item 26, 27), "ludopathy" (item 40, 41, 42, 43), and "addiction to social networks" (49, 50, 51, 52, 53, 54, 55, 56, 57). The "addiction to social networks" factor was further divided into the following sub-factors: "Addiction to Facebook" (item 61-75), "addiction to Twitter" (item 76-86), and "addiction to Instagram" (item 86-97). The factor scores were calculated as the sum of the scores obtained in each item divided by the maximum score in percentage. We established the answer 4 (between 4 and 6 hr/d) or 5 (> 6 hr/d) of item 2 "time spent online". As the cut-off points to identify the presence of, respectively, possible or certain/severe PIU, in agreement with current literature, although controversies do exist[8]. In no way it was possible to identify the participants whose anonymity was warranted.

Data collection procedure

The link for QUNT was communicated to the offices in charge of the territorial outpatient's services for drug-addicted individuals, SERTs, located in the Calabria region, in order to ask their patients to fill it in. A total of 1500 subjects were asked to

fill in the questionnaire on a voluntary basis. The present study was approved by the Ethics Committee at Pisa University.

Statistical analysis

The independent *t*-test was applied to compare the mean scores of the factors on the basis of these variables: Sex (M/F); single (yes/no living together (yes/no). One-way analysis of variance followed by Bonferroni's test for *post-hoc* was used to assess the comparisons of body mass index (BMI) categories. The χ^2 analysis was used to compare categorical variables. All statistics were carried out by the Statistical Package for Social Sciences (SPSS), version 22 (Armonk, NY, United States)[36].

RESULTS

Characteristics of the study population

The returned questionnaires numbered 183, of which 148 (80.87%) were from men and 35 (19.13%) were from women, out of the total 1500 invitations. The majority of the subjects (86, 47%) had completed 8 years of school, 73 (39.9%) the high school, 14 (7.7%) 5 years of primary school, and 10 (5.5%) were graduated. Ninety-two (50.3%) subjects were single, 64 (14.8%) were married, and 27 (14.8%) were involved in a love relationship. The mean length of attendance at the public rehab center was between 1 and 60 mo (mean ± standard deviation (SD): 32 ± 20).

Types of substance abuse and/or behavioral addiction

The most abused drugs were heroin or opioids (n = 88, 48.1%), alcohol (n = 55, 30.1%), cannabis (n = 20, 9.8%), cocaine (n = 17, 7.7%), and amphetamines (n = 3, 1.6%). Polydrug abuse (amphetamine, cannabis, cocaine, ecstasy) was present in nine (4.9%) individuals, while gambling disorder was diagnosed in 18 (9.3%). All 183 subjects were heavy smokers (Table 1).

The smartphone was found to be the most common device utilized by all subjects to access the Internet. The time spent online was similar in men and women, 4.12 ± 2.9 h. Interestingly, the time spent online by 30% of cocaine and 25% of cannabis users was significantly higher (> 6 h) than that of the other groups.

QUNT factors and gender

The distribution of the QUNT factors was not different in the two sexes; however, men using cannabis showed a trend towards higher scores (mean ± SD) at the following factors: "Social withdrawal" (2.44 ± 0.38 *vs* 2.23 ± 0.39, $P < 0.001$) and "abstraction from reality" (3.12 ± 1.74 *vs* 2.24 ± 0.46, $P < 0.001$). Cocaine users showed a higher score than the other subjects at the "loss of control" (3.64 ± 1.12 *vs* 2.51 ± 0.36, $P < 0.001$), "pornography addiction" (3.59 ± 1.44 *vs* 2.54 ± 0.41, $P < 0.001$), and "addiction to social networks" (3.22 ± 0.98 *vs* 2.66 ± 0.76, $P < 0.001$) factors.

QUNT factors and affective relationship

The analysis of the difference in QUNT factors regarding being single (n = 92) or involved in a love relationship (n = 91) showed that single subjects had higher scores at the following factors (mean ± SD): "Time spent online" (2.95 ± 0.47 *vs* 2.17 ± 0.44, $P < 0.001$); "social withdrawal" (1.40 ± 0.35 *vs* 1.34 ± 0.32, $P < 0.001$); "abstraction from reality" (1.90 ± 0.40 *vs* 1.56 ± 0.62, $P < 0.001$); "addiction to pornography" (3.12 ± 0.88 *vs* 1.99 ± 0.79, $P < 0.001$); and "addiction to social networks" (2.89 ± 1.08 *vs* 2.06 ± 0.33, $P < 0.001$).

The analysis of the differences between partners living (72) or not living together (17) with the partner showed some significant differences. The following factors showed higher scores in subjects who did not live with the partner *vs* those who lived with the partner: "Time spent online" (3.03 ± 0.53 *vs* 2.16 ± 0.76, $P < 0.001$), "addiction to pornography" (3.15 ± 0.99 *vs* 2.33 ± 0.71, $P < 0.001$), "ludopathy" (3.42 ± 1.08 *vs* 2.96 ± 0.66, $P < 0.001$), and "addiction to social networks" (2.99 ± 0.91 *vs* 2.01 ± 0.44, $P < 0.001$).

QUNT factors and BMI

The total sample was then subdivided according to the BMI values. Fifteen subjects had a BMI below 18.50 (underweight, UW), 69 between 18.51 and 24.9 (normal weight, NW), 60 between 25 and 30 (overweight, OW), 26 between 30.1 and 34.9 (first degree of obesity, OB1), and 13 greater than 35 (second degree of obesity, OB2). The categories OB1 and OB2 were merged in the category "Obese" (OB). The comparisons of QUNT factor scores in the four BMI categories are reported in Table 2, which shows that the greater the BMI values the greater the scores. Moreover, as shown in Figure 1, as BMI increased the percentage scores of the five factors, "time spent online", "social

Table 1 Types of substance abuse and/or behavioral addiction

	n (%)
Heroin or opioids	88 (48.1)
Alcohol	55 (30.1)
Cannabis	20 (9.8)
Cocaine	17 (7.7)
Amphetamines	3 (1.6)
Polydrug abuse	9 (4.9)
Gambling disorder	18 (9.3)
Smokers	183 (100)

withdrawal", "abstraction from reality", "ludopathy", and "addiction to social network", also trended upward. Finally, fifteen of the total cocaine users were also pathological gamblers (mainly online gamers) and showed a significantly higher score at the "ludopathy" factor (3.20 ± 0.45 *vs* 2.86 ± 0.51, $P < 0.001$).

DISCUSSION

The present study reports the results of a collaborative survey investigating the prevalence and characteristics of Internet use by new technologies (PCs, smartphones and tablets), as well as of PIU, amongst subjects undergoing a program of rehabilitation in public rehab centers in a region from southern Italy. According to our knowledge, this is the first study carried out in this peculiar adult population, as previously only samples of adolescents were investigated[37].

Several subjects received the invitation from their psychiatrists/psychologists to fill in a questionnaire, the so-called QUNT, which was developed by us for this purpose. The specificity of the QUNT, as compared with those utilized in different studies, is that it is very detailed in order to assess the variety of individual features of both Internet use and PIU. The item 2 "time spent online" was considered crucial to identify the possible presence of PIU when it was between 4 and 6 hr/d (answer 4), or of severe PIU, when it was > 6 hr/d (answer 5).

About 10% of the subjects returned the QUNTs correctly filled in that were valid for statistical analyses. This can be ascribed to the peculiar personality of drug addicts, especially chronic ones that represent the majority of our sample, and it would indicate both a low propensity to collaborative studies and compliance as well as amotivation[38]. The most used device (100% of subjects) to access the Internet was the smartphone. There was a high preponderance of men over women, which reflects the distribution of sexes in public rehab centers in Italy, in agreement with national data showing that the ratio male:female is 4:1[39].

All subjects were heavy smokers, almost 50% of them used heroin and/or opioid compounds, 30% alcohol, 10% cannabis, 8% cocaine, and 5% were polydrug users. Only three subjects were amphetamine users and, therefore, were not included in the statistical analyses. Almost 10% of individuals were also suffering from gambling disorder, while the presence of other psychiatric disorders was set as an exclusion criterion.

The time spent online was quite high, more than 4 hr/d in the total sample, with a slight, albeit not significant prevalence in male subjects. Cocaine and cannabis users spent more than 6 hr/d online, significantly more than opioid and alcohol abusers. Therefore, they were probably affected by a severe PIU, according to the setpoint defined by us (answer 5 of item 2) and literature data[12,40-42]. Taken together, these findings indicate that although PIU is possibly present in all categories of drug addicts, it is less severe in subjects taking sedative substances, such as heroin/opioids and alcohol. Alternatively, it may be used as a "stimulant" trigger in cocaine and cannabis users. This is supported by the high prevalence of gaming disorder amongst cocaine abusers, in agreement with literature data[43-45].

The analysis of the distribution of the QUNT factors showed no sex-related differences and a slight trend towards higher scores at the "social withdrawal" and "abstraction from reality" items in men. This is in contrast with a previous study carried out in healthy subjects that revealed significant differences between men and women. A possible explanation might be the flattening effects of abused drugs that tend to "minimize" sex differences[46]. As compared with the other groups, cocaine

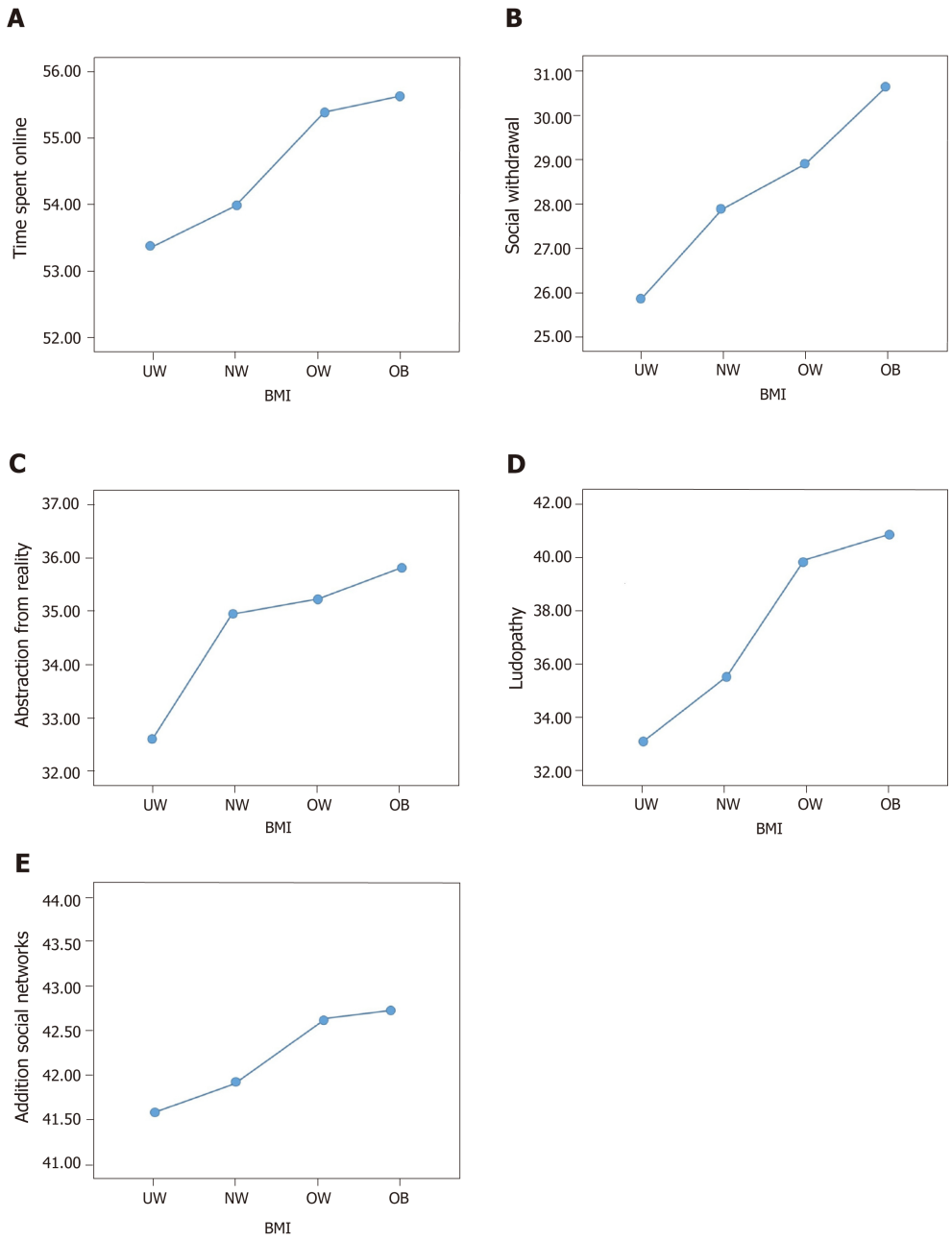

Figure 1 Trend of the percentage scores of some QUNT factors and body mass index. A: Time spent online; B: Social withdrawal; C: Abstraction from reality; D: Ludopathy; E: Addiction to social networks. BMI: Body mass index; UW: Underweight; NW: Normal weight; OW: Overweight; OB: Obesity; QUNT: Questionario sull'Utilizzo delle Nuove Tecnologie.

users showed higher scores at the "loss of control", "pornography addiction", and "addiction to social networks" factors. This is not surprising given the stimulant effect of this substance[47].

Our findings confirmed the "protective" effects of a love relationship and/or living together with a partner[48], as single subjects or those living alone with no family support showed higher scores on different items, specifically "time spent online", "social withdrawal", "abstraction from reality", "addiction to pornography", and "addiction to social networks". This clearly indicates that Internet was mainly used for passing time or recreation.

Not surprisingly, those subjects who spent more time online, as shown by the higher score of the "time spent online", "social withdrawal", "abstraction from reality", and "addiction to social network" factors, had a higher BMI. Therefore, the excessive use of the Internet can be considered another factor that increases sedentary behaviors[49], and it may be particularly risky in drug addicts who are already more vulnerable subjects already exposed to different medical diseases[50]. Reduced sleeping time and altered circadian rhythms due to PIU are other factors that may increase the

Table 2 Comparisons of the QUNT factor scores in the four BMI categories

Factors	UW	NW	OW	OB	*F*	*P* value	*Post-hoc* comparison:Significantfor *P* < 0.05
Time spent online	53.44 ± 13.68	53.80 ± 13.12	54.91 ± 12.71	55.83 ± 14.10	3.87	0.009	OW > UW
Social withdrawal	25.39 ± 6.35	27.55 ± 7.61	28.73 ± 8.94	30.81 ± 10.14	9.91	0.001	OW > UW; OB > UW; OB > NW
Abstraction from reality	32.33 ± 10.02	34.90 ± 10.13	35.11 ± 12.98	36.11 ± 13.44	2.69	0.045	None
Loss of control	28,10 ± 9.11	29.79 ± 10.11	31.04 ± 12.49	31.21 ± 10.87	1.95	1.98	None
Addiction to pornography	43.32 ± 12.28	41.95 ± 13.70	41.34 ± 11.03	42.09 ± 13.45	1.55	0.250	None
Ludopathy	33.26 ± 13.17	36.23 ± 10.85	39.88 ± 22.91	41.16 ± 22.39	4.28	0.005	OW > NW
Addiction to instant messaging	54.05 ± 18.33	56.02 ± 16.47	56.24 ± 18.36	55.60 ± 17.09	1.72	0.197	None
Addiction to social networks	41.60 ± 12.61	42.13 ± 13.15	41.80 ± 12.19	44.14 ± 18.90	1.81	0.187	None

QUNT: Questionario sull'Utilizzo delle Nuove Tecnologie; BMI: Body mass Index; UW: Underweight; NW: Normal weight; OW: Overweight; OB: Obesity.

probability of metabolic, medical, and psychiatric disorders[11,16,51] as well as of a disruption of work, family, social, or school performance[52,53].

Finally, the majority (15 out of the total 17) of cocaine users were also pathological gamblers (mainly online gamers), and showed a significantly higher score at the "ludopathy" factor. This would suggest a specific vulnerability of drug addicts to other kinds of addictions, especially if they use stimulants rather than sedative drugs[43]. Our study has some limitations that should be acknowledged. The QUNT questionnaire was not validated, although this is quite common in studies in this field[12,40-42]. The prevalence of PIU was inferred from one item only, but it was a corollary of the main objective of the study exploring primarily the characteristics of Internet use. Similarly, no information was gathered on emotional distress or disturbed behaviors that are currently under investigation.

Taken together, our results suggest that the excessive use of Internet through smartphones is very common in drug addicts, as shown by their time spent online, and that PIU is very common in these individuals, especially in those taking cocaine and cannabis. The relationship between time spent online (and related sedentary lifestyle) and BMI would suggest that Internet use might be a contributing factor for increased weight and obesity amongst adolescents and young adults world-wide[49,54]. Our findings would suggest specific vulnerability of drug addicts, mainly if they use stimulants rather than sedative compounds, not only to other kinds of pharmacological but also to behavioral addictions, such as PIU or pathological gaming. Prevention of addictions should take into consideration the novel, and still poorly explored, domain of behavioral addictions, especially of PIU that today represents a worldwide epidemic[12,54-56].

ARTICLE HIGHLIGHTS

Research background

Problematic Internet use (PIU) is a novel behavioral addiction characterized by excessive Internet use that is becoming an increasing problem worldwide. Although no agreement exists on precise diagnostic criteria, PIU is considered a behavioral addiction sharing with substance use disorders (SUDs) and other addictions several features and perhaps neurobiological underpinnings.

Research motivation

Unfortunately, no information is available on the prevalence of PIU amongst drug-addicted subjects, in spite of the given evidence, that these individuals tend to be affected by polydrug use and also by behavioral addictions, as if the presence of one or more addictions would represent a sort of vulnerability towards a worsening of the clinical picture through the onset of other kinds of these disorders.

Research objectives

The investigation of the possible existence and prevalence of PIU amongst drug-addicts under treatment in rehab centers would permit the implementation of specific treatments to prevent the onset of other kind of addictions that could worsen the clinical picture and the rehabilitation programs.

Research methods

A specific questionnaire to be filled online, the so-called Questionario sull'Utilizzo delle Nuove

Tecnologie (QUNT), was developed to explore the prevalence and characteristics of both Internet use and PIU. The QUNT consists of two sections, one for demographic data and another consisting of 101 items grouped in factors built according to *a priori* criteria extrapolated from the data available in scientific literature. All subjects who volunteered to participate in the study (n = 183) reported that the QUNT was useful and were satisfied with it. The factor scores were calculated as the sum of the scores obtained in each item divided by the maximum score in percentage. We chose the answer 4 (between 4 and 6 hr/d), and the answer 5 (> 6 hr/d) of item 2 "time spent online". In order to identify the body mass index (points for, respectively, the possible or certain (and severe) presence of PIU.

Research results

The time spent online was more than 4 hr/d in the total sample, with a slight, although not significant, prevalence amongst male subjects. Cocaine and cannabis users spent more than 6 hours online, significantly more than opioid and alcohol users. The distribution of the QUNT factors was not different in both sexes. Cocaine users showed higher scores at the "loss of control", "pornography addiction", and "addiction to social networks", probably because of the stimulant effect of this substance. Moreover, 15 out of the total 17 cocaine users were also pathological gamblers. Positive and statistically significant relationships were also observed between some QUNT factors and body mass index (BMI). These results, while showing that PIU is common amongst stimulant drug abusers, require to be replicated in larger samples from other countries. Nevertheless, they underline the risk of behavioral addictions in drug addicts, a problem that should be taken into account when planning prevention and intervention strategies.

Research conclusions

The new findings of this study are represented by the large percentage of PIU amongst drug addicts, especially if they use cocaine or cannabis. This suggests that, although the abuse of Internet is present in all drug addicts, PIU is less common in subjects taking sedative substances, such as heroin/opioids and alcohol, while it may become a sort of "stimulant" trigger in cocaine and cannabis users, as supported by the high prevalence of pathological gaming amongst cocaine abusers. Further, PIU is more frequent in single subjects or subjects living alone, a result stressing the protective effects of loving or social relationships in general against the onset of addictions. Those subjects who spent more time online, as shown by the higher score of the "time spent online", "social withdrawal", "abstraction from reality", and "addiction to social network" factors, had a higher BMI. Therefore, the excessive use of the Internet can be considered as another factor increasing sedentary behaviors that may be particularly risky in drug addicts, subjects already prone to different medical diseases. Reduced sleeping time and disrupted circadian rhythms due to PIU are other factors that may increase the probability of metabolic, medical, and psychiatric disorders as well as the impairment of work, family, social, or school performance.

Research perspectives

The findings of the present study indicate that behavioral addictions, such as PIU, can broaden polydrug use, especially in subjects taking stimulants or cannabis. In addition, PIU may be considered another factor increasing negative life habits, already impaired in drug addicts, while promoting sedentary behaviors and maladjustments in different individual's domains. Future studies should take into consideration the impact of PIU on drug addicts by means of specific instru-ments to assess it, in order to prevent, not only its detrimental consequences, but also those related to a broadening of addictive behaviors.

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