Chapter 14
Pharmacological Treatment of Internet Addiction

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Abstract The increasing number of Internet users has resulted in an increased population percentage affected by the negative effects of problematic Internet usage. To date, the management of psychopathological Internet use is not supported by extensive empirical research. No standard clinical treatment protocols for pharmacological treatment exist, and as a result, empirical or anecdotal assessments based on case studies are mainly consulted. A relevant problem in performing clinical trials is the evolving nosology, which encompasses ambiguous definitions of Internet addiction and a diversity of diagnostic, prognostic, and therapeutic criteria. The aim of this chapter is to review the current literature, to assess the extent to which specific pharmacological interventions (e.g., using antidepressants, mood stabilizers, opioid receptor antagonists, or antipsychotics) can alleviate the symptomatic burden in patients with "Internet addiction." We also explore pharmacological interventions that target patterns of comorbidity and underlying psychopathological dimensions (e.g., addiction, impulsivity, obsessive-compulsive spectrum, bipolar spectrum, dissociation, etc.) shared with other behavioral or substance addictions.

Keywords Internet addiction · Comorbidity · Pharmacological treatment

14.1 Introduction

The Internet represents one of the most important products of culture and industry in society and has become an integral part of daily life for many people. Worldwide, more than one billion computers are connected to the Internet (Reuter et al. 2005)

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and the increasing number of Internet users has, in fact, resulted in an increased percentage of users being afflicted by problematic Internet use. This phenomenon is growing, both in terms of prevalence and within the public consciousness, as a pathological condition. This societal development together with an increase in clinical observations, raise issues concerning the management of the condition. To date, there is no consensus in the literature with respect to the definition of problematic Internet use, though most authors refer to it as "Internet Addiction" (IA) (Tao et al. 2010).

The study of IA is currently hampered by ambiguous definitions of the phenomenon and a diversity of diagnostic, prognostic and therapeutic criteria. Internet use can lead to a state that appears to meet the Diagnostic and Statistical Manual of Mental Disorders (DSM) definition for a mental disorder, described as "a clinically significant behavioral or psychological syndrome associated with present distress or with a significantly increased risk of suffering death, pain, disability or an important loss of freedom" (APA 2013). No clinical conditions related to problematic Internet use have been part of any diagnostic system, until now. Considerable effort has been made to include "Internet addiction," "pathological Internet use," "problematic Internet use" (Shapira et al. 2000) or any of its derivatives in the 2013 update of the Diagnostic and Statistical Manual of Mental Disorders, the Fifth Edition (DSM-5), but no official criteria exist in either the DSM-5 or in the International Classification of Diseases, Tenth Revision (WHO 2010). To date, only "Internet gaming disorder" has been included in Sect. 14.3 of DSM-5 (American Psychiatric Association 2013), and the core feature of this disorder is the persistent and recurrent participation in computer gaming, typically massively multiplayer online role play games, for many hours. This condition is included to reflect the scientific literature (most of which comes from studies in Asian countries) on persistent and recurrent use of Internet games, and preoccupation with these, which can result in clinically significant distress and functional impairment of general life, such as social interaction, academic performance, occupational interest, and behavioral problems (Petry and O'Brien 2013). As a syndrome listed in Sect. 14.3 of DSM-5, "Internet gaming disorder" requires further research before it can be formally considered as a disorder in its own right.

Although the diagnostic criteria and assessment questionnaires used for diagnosis may vary between countries, surveys in the United States and Europe indicated that IA may affect between 1.5 and 8.2% of the general population (Weinstein and Lejoyeux 2010). To date, clinicians have only empirical or anecdotal reports at their disposal, concerning pharmacological treatment options for the management of the large number of patients suffering from IA. For this reason, in our chapter we review the role of pharmacotherapy in the treatment of IA to guide clinical decisions according to the most recent data. We also provide a psychopathological framework for this particular form of behavioral addiction, with the intention of proposing a guided approach to aid clinicians in choosing between available drugs.

14.1.1 Is Pharmacological Treatment a Valid Therapeutic Option for IA?

In order to provide an answer to this question, an overview of the empirical data on functional changes occurring in the brains of patients suffering from non-substance related addictions is of relevance. The identification of specific neurophysiological dysfunction in behavioral addictions would establish a biological rationale for intervention. Data to this effect are scarce in the literature.

The potential phenomenological overlap between IA, substance addiction and, in particular, gambling suggests that a common neurobiological substrate involving an impairment of the "reward system" underlies these disorders. The mesolimbic dopaminergic pathway represents the final common pathway for reinforcement/reward induced by physiological stimuli or psychotropic drugs. It follows that dopamine is considered the neurotransmitter responsible for mediating "pleasure" (Di Chiara and Bassareo 2007). The intake of certain substances or the execution of certain behaviors, induces a very intense and fast feeling of pleasure (consummatory pleasure) caused by the rapid increase of dopamine in the mesolimbic system (Di Chiara and North 1992). Moreover, dopamine is also elevated when anticipating the substance use or behavioral execution (anticipatory pleasure) and this also drives motivational processes that promote goal-directed behaviors aimed at achieving desired rewards. Addiction disrupts the normal activity of these dopaminergic circuits, thus redefining the hierarchy of motivational priorities.

In this regard, the literature provides small, but convincing evidence for a link between biological brain abnormalities in patients addicted to substances and similar brain abnormalities in patients with IA. Blum et al. (2012) persuasively linked a reward-deficient aberrant behavior (RDAB) to abnormal dopaminergic function in the nucleus accumbens, and argued that RDABs can be observed both in conventional substance-use disorders, and also in excessive internet gaming and related activities that stimulate excessive dopamine release, such as gambling.

Several fMRI studies in pathological gamblers have reported blunted neural responses to appetitive cues, primarily in ventral striatum and orbital/lateral prefrontal cortex (Reuter et al. 2005; de Ruiter et al. 2009; Balodis et al. 2012) and these observations have been interpreted in terms of the reward deficiency hypothesis of addiction.

Furthermore, a neuroimaging study conducted by Ko et al. (2009) suggested that both the strong desire to play online video games[1] and craving, e.g., for nicotine/alcohol in substance dependent addictions could be explained by a single neurobiological mechanism. The right orbitofrontal cortex, the medial frontal cortex, the anterior cingulate cortex bilaterally, the right dorsolateral prefrontal cortex, the caudate nucleus and the right nucleus accumbens were activated when patients were stimulated with images of "online gaming" in contrast to a neutral picture

[1]Characterizing a particular form of IA, namely "online game addiction".

condition. These imaging results suggest that "online gaming addiction" indeed shares biological substrates with substance addiction. For instance, the urge to smoke cigarettes while watching a videotape showing smoking scenes in current smokers was associated with increased metabolic activity in the ventral striatum, anterior cingulate, orbitofrontal cortex, middle temporal lobe, hippocampus, insula, midbrain and thalamus (Weinstein et al. 2010).

From this it could be intuitively derived that IA might be treatable in the same way as other addictions. In 2010, Liu et al. (2010) carried out a functional magnetic resonance imaging (fMRI) experiment, by using the regional homogeneity (ReHo) method to analyze cerebral function characteristic of IAD college students under resting state. In adolescents with IAD, compared to healthy controls, they found that the increased ReHo brain regions (representing the increase in cerebral metabolic rate) were distributed over the cerebellum, brainstem, limbic lobe and frontal cortex, indicating a possible involvement of the "reward" system.

Summing up the evidence, to date the knowledge on the neurobiological underpinnings of IA is extremely limited and is insufficient as a basis for pharmacological intervention. Nevertheless, if we assume that a malfunction of the reward system underlies IA, one might conclude that pharmacological interventions of use in treating other forms of addiction may be eligible as a starting point for psychopharmaceutical research in the area of IA.

14.2 Clinical Evidence on Pharmacotherapy for IA

To date, case studies of IA treatment are rather scarce and several key limitations have been highlighted, including inconsistencies in definition and diagnosis, a lack of randomization and blinding techniques, a lack of adequate controls or other comparison groups, and insufficient information concerning recruitment dates, sample characteristics, and treatment effect sizes (King et al. 2011).

First, we reviewed the current literature on pharmacotherapy specifically for "Internet addicted" patients. However, considering the lack of adequately large, rigorous studies, we also focused, in a second step, on the underlying psychopathological dimensions of IA (i.e., impulsivity, compulsivity, craving, obsessive-compulsive spectrum) as well as on the high prevalence of comorbid conditions to address the issue of dual diagnosis.

We discuss the clinical evidence available for different classes of psychotropic drugs, according to our recent article (see Camardese et al. 2012).

14.2.1 Antidepressants

Antidepressants are psychotropic drugs mainly used in depression, dysthymia and anxiety. They include: monoamine oxidase inhibitors, tricyclics, selective serotonin

reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors and melatonergic agents. The onset of the antidepressant effect is delayed (4–8 weeks) and treatment typically lasts for months or years. They determine mood enhancement, alertness and attention, increased appetite, regularization of sleep and reduction of the hypochondriac attitude. Moreover, serotonergic antidepressants have been proven to be helpful to alcoholics in maintaining abstinence and decreasing craving for alcohol in detoxified alcohol dependent subjects (Janiri et al. 1998). Bupropion (a dopamine/norepinephrine reuptake inhibitor) is also effective for smoking cessation (Hughes et al. 2007).

The use of antidepressants for IA, in particular SSRIs may be endorsed mostly by evidence of the aminergic systems' role in the suppression of inhibitory control (i.e., "resisting" the urge) and the control of compulsive repetition, as well as data indicating a high lifetime prevalence of major depression in "internet addicts" (Shapira et al. 2003; Yen et al. 2007; Lee et al. 2008). Clinical studies have also suggested a close relationship between serotonergic dysregulation, impulsivity, and symptoms of the obsessive-compulsive spectrum, for which serotonergic drugs are known to be effective (Goddard et al. 2008). However, while definitely effective in treating obsessive-compulsive disorder, SSRIs have shown mixed results in some impulse control disorders, namely pathological gambling, kleptomania and compulsive shopping (Kim et al. 2002; Koran et al. 2002, 2007; Grant et al. 2009).

The first experience reported in the literature on IA concerns treatment with escitalopram (a SSRI) in an "internet gaming addicted" patient (30 mg/day for 3 months). An improvement in mood and a significant reduction of the strong urge to perform online gaming were observed, leading to a complete functional recovery (Sattar and Ramaswamy 2004). Another study investigated the effectiveness of escitalopram (20 mg/day for 10 weeks) on 19 "Internet addicts" (Dell'Osso et al. 2008). During the 10 week open-label phase,[2] 11 patients (64.7% of the sample) showed significant decreases in weekly hours spent online and improvements in global functioning. At the end of the 10 weeks, subjects were blindly randomized to either continued escitalopram treatment or to placebo. The abovementioned improvement persisted in the second phase of the study, but no significant differences were observed between those who continued taking the drug and those who were switched to placebo. The authors speculate that 9 weeks may not have been sufficient for the effect to be lost in the placebo group, or for additional gains to be made in the escitalopram group, but also do not rule out the possibility that the improvements seen in the open-label phase may have been a placebo response.

A study on 11 "Internet game addicted" patients and 8 healthy controls, assessing brain activity in response to a game stimulus using functional magnetic resonance imaging (fMRI), explored the possible effectiveness of bupropion, a norepinephrine/dopamine reuptake inhibitor. Patients showed higher activation in the left occipital lobe, left dorsolateral prefrontal cortex and left parahippocampal gyrus before treatment. After 6 weeks of treatment, craving for Internet video game

[2]A clinical trial where both physician and patient know about the administered drug.

play, total game play time, and cue-induced brain activity in the dorsolateral prefrontal cortex were decreased (Han et al. 2010). This allowed the authors to presume that the drug was effective but, given the small sample size, further studies are needed to support this assumption.

A study conducted on Internet addicts with comorbid major depressive disorder and excessive online game play, further investigated the role of bupropion in reducing the severity of online game play as well as depressive symptoms (Han and Renshaw 2011). The study consisted of a 12-week, randomized, double-blind clinical trial, including an 8-week active treatment phase and a 4-week post-treatment follow-up period. Significant bupropion-associated reductions in online gaming and depressive mood were observed, though the latter improvement did not persist during the post-treatment follow-up period.

The anti-craving properties of antidepressants still need to be evaluated with respect to long-term outcomes and in controlled studies. Regarding observations on anti-craving properties made in other addiction research, evidence for short-term effects seems to exist in the main. Long-term exposure to antidepressants may also facilitate mood swings toward the manic pole, to which subjects with pathological addictions seem more prone (Goldberg and Whiteside 2002). This could imply a greater risk of relapse of impulsive behavior, which is characteristic of manic mood.

14.2.2 Opioid Receptor Antagonists

Opioid receptor antagonists such as naltrexone and nalmefene block the reinforcing effects of opioids and reduce substance consumption and craving. Generally, they have no abuse potential, mild and transient side effects, and appear to be a suitable treatment for addiction in combination with psychosocial support. Opioid receptor antagonists are mainly prescribed in alcoholism and heroin dependence.

Various studies have found a high comorbidity rate between IA and other forms of addiction (such as a substance use disorder) as well as impulse control disorders (Bernardi and Pallanti 2009). In this regard, Griffiths (2000) suggested that the Internet merely represents a different context in which gamblers, shopping addicts and sex addicts develop their pathological behavior. In particular, Davis (2001) distinguished a "specific pathological Internet use" and a "generalized pathological Internet use." The first includes online sexual material/services, online auction services, online stock trading and online gambling. These dependencies are content-specific and they would exist in the absence of the Internet and in a manner independent of multiple Internet functions. The second involves a general, multidimensional overuse of the Internet and it may be related to the social aspect of the Internet. Individuals with general pathological Internet use are considerably more problematic, in that their pathology would likely not even exist in the absence of the Internet (Davis 2001).

In our opinion, the mounting evidence on pathological gambling considered by the authors could equally be applied to some IA patients, given that gambling

shares, as previously mentioned, the conceptual and phenomenological bases of a behavioral addiction. The psychopathological (e.g., impulsivity, compulsive repetition, etc.) overlap between IA, substance addiction and pathological gambling suggests a common neurobiological substrate, involving a dopamine dysfunction of the neural "reward systems." Opioid receptor antagonists inhibit dopamine release in the nucleus accumbens and ventral pallidum and have been considered for use in some behavioral addictions. Literature is currently limited to a single case report in the treatment of IA with opioid receptor antagonists (see Bostwick and Bucci 2008). This case study reported successful treatment with naltrexone, which has also proven effective in the treatment of other impulse control disorders, such as pathological gambling and kleptomania (Grant et al. 2008, 2009). The patient in this study was a 31-year-old male with compulsive cybersexual behavior (chatting online, masturbating for hours, and occasionally, sex with Internet contacts). A stable dose of sertraline was ineffective in treating his "Internet addiction". Naltrexone (150 mg/day) was gradually administered and helped to induce a 3-year remission. The authors hypothesize that by blocking the capacity of endogenous opioids to trigger dopamine release in response to reward, naltrexone may block the reinforcing nature of compulsive Internet sexual activity.

14.2.3 Mood Stabilizers

Mood stabilizers are drugs that have the property of acting on mood. They affect long-term mood stability and typically lead to an improvement of the initial condition (e.g., depression, anxiety, agitation, etc.). Mood stabilizers, such as lithium or anticonvulsants (e.g., valproic acid, carbamazepine and lamotrigine), are primarily used to treat bipolar disorder (BD). On the other hand, non-mood stabilizing anticonvulsants (e.g., gabapentin and pregabalin) are also increasingly used to treat alcoholism and substance abuse disorders. Generally, they show a safe side-effect profile and are well tolerated by patients (Guglielmo et al. 2012).

A potential use for mood stabilizers in the treatment of IA may be substantiated by similarities between mood disorders belonging to the bipolar spectrum and IA. Both conditions are characterized by impulsive behaviors (mainly during manic episodes in bipolar patients) and often coexist. In particular, a high lifetime prevalence (up to 70%) of bipolar disorder has been found in Internet addicted patients. (Shapira et al. 2003; Di Nicola et al. 2010b).

A specific anti-compulsive property of some mood stabilizers has been hypothesized. Lithium and anticonvulsants have, in fact, been successfully used in the treatment of various impulse control disorders (Roncero et al. 2009). Likewise, in patients with substance use disorders, valproate appears to be a potentially fruitful medication due to its anti-craving property (Maremmani et al. 2010). Furthermore, there is data pointing to the considerable utility of mood stabilizers (particularly lithium and valproate) in the treatment of pathological gambling (Pallanti et al. 2002). At present, the effectiveness of mood stabilizers in the

treatment of IA has not been investigated, though consideration of this drug class in future studies is certainly promising.

14.2.4 Antipsychotics

Antipsychotics include drugs used for the treatment of psychotic diseases, such as schizophrenia or bipolar disorder, mainly acting on neurotransmitter systems of dopaminergic and serotonergic pathways. Antipsychotics can be divided in first-generation antipsychotics (typical antipsychotics or neuroleptics) and second-generation antipsychotics (atypical). The main difference is that typical antipsychotics have a highly selective affinity for D2 receptors while atypical antipsychotics can modulate both dopaminergic and serotonergic systems in different ways. Due to their relevant action on dopamine receptors of the nigrostriatal pathway, neuroleptics increase the risk of extrapyramidal effects, unlike atypical antipsychotics, which are more tolerable in terms of neurological side effects. On the other hand, due to their particular pharmacodynamic properties, atypical antipsychotics are also frequently used in other clinical conditions like mood disorders, anxiety, and autism spectrum disorders.

With respect to these drugs, possible models for their use in patients with addiction are linked with antipsychotics' effectiveness in the treatment of resistant obsessive-compulsive disorder (Choi 2009). Given their serotonergic properties, atypical antipsychotics have been most investigated. Prescription of atypical antipsychotics seems to be a highly helpful strategy for treatment-resistant obsessive-compulsive disorder, with benefits most evident for risperidone (Bloch et al. 2006). Authors of several placebo-controlled clinical trials have found evidence to support psychopharmaceutical treatment with olanzapine (Bystritsky et al. 2004), risperidone (Hollander et al. 2003) and quetiapine (Denys et al. 2004). Head-to-head comparisons involving these agents have also been conducted: Maina et al. (2008) compared olanzapine and risperidone augmentation in subjects resistant to SSRIs and found that both were equally effective at reducing obsessive-compulsive symptoms. In particular, medication augmentation refers to the addition of a second drug to an initial, ineffective pre-existing therapy. A single pilot trial of atypical antipsychotic monotherapy using aripiprazole has also been published (Connor et al. 2005), with significant improvement observed, particularly in compulsive symptoms. Moreover, preliminary data also support a possible efficacy of aripiprazole in reducing alcohol craving (Martinotti et al. 2007, 2009).

The use of antipsychotics in treating impulse control disorders has also been investigated, given that the central features "impulsivity" and "compulsive repetition" are possible targets for antipsychotic medication. In particular, preliminary studies have shown that olanzapine, targeting both dopaminergic and serotonergic functioning, effectively reduces impulsivity. Olanzapine has shown preliminary effectiveness in several disorders in which a lack of impulse control is a key feature, such as trichotillomania, skin picking, and borderline personality disorder

(Garnis-Jones et al. 2000; Stewart and Nejtek 2003; Christensen 2004; Shoja-Shafti 2006). Each of the clinical conditions that responded to olanzapine share phenomenological features with pathological gambling, in that patients are unable to resist impulses, and act without thinking about the consequences. Olanzapine has, thus, been tested in the treatment of pathological gambling, though it did not show significant effectiveness (McElroy et al. 2008). Quetiapine has also been tested as a treatment of pathological gambling and, in addition, it has been used as an add-on treatment for the management of bipolar I disorder with comorbid compulsive shopping and physical exercise addiction (Di Nicola et al. 2010a).

Given the overlap between impulsivity/compulsivity symptoms of IA and the abovementioned psychiatric conditions, it has been hypothesized that antipsychotic treatment could benefit "Internet addicted" patients. A promising case study reported the successful use of quetiapine (200 mg/day), gradually added to citalopram, in a 23-year-old subject with IA (Atmaca 2007). The improvement was maintained at a 4-month follow-up.

14.2.5 Other Drugs

Future research on the pharmacological treatment of IA should also consider focusing on further drug categories, namely psychostimulants, alpha-2-adrenergic agonists (commonly referred to as alpha 2 agonists) and glutamatergic drugs.

Among these, psychostimulants (i.e., methylphenidate) are the only class for which anecdotal data is available in relation to a possible use in "internet addicted" patients. Methylphenidate (MPH) is a stimulant molecule, indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adults. It can also be used to treat chronic fatigue syndrome or symptoms of traumatic brain injury and daytime symptoms of fatigue induced by narcolepsy.

Recently, one trial tested methylphenidate in 62 attention deficit/hyperactivity disorder (ADHD) subjects with "Internet video game addiction," reporting a significant improvement both in attentional capacity and in Internet usage after 8 weeks of treatment (30.5 mg/day) (Han et al. 2009). The authors cautiously suggest that methylphenidate may be beneficial as a treatment for IA, especially where it co-occurs with ADHD. In fact, many clinical studies provided evidence for a link between ADHD and "Internet addiction," with comorbidity rates reaching up to 33% (Yoo et al. 2004). This comorbidity suggests that other drugs used to treat ADHD patients could also be considered as avenues for possible treatment, at least for the subgroup of "Internet addicts" also suffering from ADHD. For instance, alpha 2 agonists, recently approved in controlled release formulations for ADHD, have anecdotally been found to act on impulsive behavior. In fact, among alpha 2 agonists, Guanfacine extended-release has demonstrated effectiveness in reducing impulsivity, hyperactivity and inattention in children and adolescents suffering from ADHD (Muir and Perry 2010). Likewise, there is evidence supporting the use of clonidine extended-release (another alpha 2 agonist) in the treatment of ADHD

youth with inadequate response to stimulants. It appears that if clonidine is used in combination with psychostimulants, it provides incremental effectiveness in improving ADHD symptoms (Kollins et al. 2011). These preliminary clinical findings demonstrating that alpha 2 agonists have beneficial effects on ADHD symptoms that overlap with those of patients suffering from IA (namely impulsive behavior), suggest they should be studied in the context as IA as well.

Finally, the rationale for glutamatergic drugs' possible use in "Internet addicted" patients is linked to the fact that, along with dopaminergic dysfunction, glutamatergic system alterations have also been implicated in the pathophysiology of behavioral and substance addictions. There are several clinical reports that support the possible effectiveness of glutamatergic modulators in treating these conditions (Krystal et al. 2003). Among glutamatergic drugs, memantine (a NMDA receptor antagonist) and riluzole (an inhibitor of glutamate synaptic release) have been mostly investigated. Preclinical and clinical observations suggest that glutamatergic modulators target obsessive-compulsive symptoms and impulsivity. Memantine appears to diminish gambling and reduce impulsive decision making in patients with pathological gambling (Grant et al. 2010a). Of note, memantine was not more effective than placebo in reducing alcohol use (Evans et al. 2007). Riluzole has been found to have beneficial effects on patients with obsessive-compulsive disorder (Grant et al. 2010b) and in the treatment of self-injurious behavior associated with borderline personality disorder (Pittenger et al. 2005). Also, riluzole has been successfully used in cases of compulsive skin picking (Sasso et al. 2006) and in a patient with severe, chronic trichotillomania (Coric et al. 2007). Though promising, most of these results are reported in small studies and case studies and, thus, their generalizability is limited. Further examination of glutamate-modulating agents in the treatment of disorders associated with impulse control dysregulation and obsessive-compulsive symptoms, including IA, would certainly be of value.

14.3 Clinical Suggestions for a Psychopathologically Guided Approach

Case studies on IA treatment are rather limited, the quality of the current literature in this emerging field is not optimal, and no standard clinical treatment protocols or approved medications yet exist.

We summarize the reported evidence in Table 14.1.

The limited existing empirical evidence does not allow for definite conclusions to be drawn. We are not yet able to determine to what extent pharmacological treatment of approved psychopathological disorders may also help in the treatment of IA. But a clinically significant beneficial effect is easily discerned and has commonly been observed in daily clinical practice.

A recent meta-analysis of psychological and pharmacological interventions for IA suggests that both forms of therapy are highly effective for improving addictive behavior, time spent online, depression and anxiety after treatment (Winkler et al. 2013).

Table 14.1 Overview of clinical evidence on pharmacotherapy for IA

Class	Drug	Dosage	Patients	Outcome	References
Antidepressants	Escitalopram	30 mg/day for 3 months	1 Internet gaming addict	Mood improvement, reduction in online gaming drive and complete recovery of functioning	Sattar and Ramaswamy (2004)
		20 mg/day for 10 weeks	19 Internet addicts	Significant decrease in weekly hours spent online	Dell'Osso et al. (2008)
	Bupoprion	300 mg/day for 6 weeks	11 Internet gaming addicts	Decrease in craving and total time spent gaming online	Han et al. (2010)
		300 mg/day for 8 weeks	50 Patients with major depressive disorder and problematic online gaming	Reduction in online gaming and depressive symptoms	Han and Renshaw (2011)
Opioid receptor antagonists	Naltrexone	150 mg/day for >3 years (in addition to sertraline 100 mg/day)	1 Patient with compulsive cybersexual behavior	Perceived control over sexual urges	Bostwick and Bucci (2008)
Antipsychotics	Quetiapine	200 mg/day for 4 months (in addition to citalopram 40 mg/day)	1 Patient with internet addiction	Lower obsessive-compulsive features and decrease in 'nonessential' internet use	Atmaca (2007)
Other	Methylphenidate	30.5 mg/day for 8 weeks	62 ADHD patients with video game addiction	Lower young internet addiction Scale scores and decrease in internet use	Han et al. (2009)

With respect to pharmacological treatment, this analysis pooled 49 subjects of three different trials using escitalopram, bupropion, and methylphenidate. Interestingly, when comparing psychological versus pharmacological interventions, the authors did not find any significant differences in the efficacy of improving status and reducing time spent online. This finding supports the hypothesis that, in the future, pharmacotherapy could significantly contribute to the management of "Internet addicted" patients, with a particularly favorable cost-benefit profile.

In order to define the actual role of pharmacotherapy in the treatment of IA, we draw primarily on the evidence obtainable from clinical practice, to consider patterns of comorbidity and to propose some considerations from a psychopathological view. The latter are mere suggestions that may contribute to the complex clinical management of many "Internet addicted" patients, who are referred to clinicians, possibly alleviating their psychic distress and encouraging supporting their adhesion to treatment and rehabilitation programs.

If the patient exhibits high levels of discomfort and craving that interfere with the treatment strategy, and substance addiction coexists, the use of an opioid antagonist could be considered.

Patients with clinically significant anxiety levels or depressive symptoms, and specifically in case of comorbidity with anxiety disorders or depression, the use of a serotonergic drug could be helpful. In the case of a comorbidity with major depression, bupropion should be considered a good option. If the patient has manic or hypomanic symptoms, or in some cases of sub-syndromic excitement, the clinician could also consider the use of mood stabilizers, taking into account that their effectiveness in "internet addiction" has not yet been investigated.

To date, the research on IA is mainly focused on diagnostic criteria and assessment instruments (there is a significant need for consensus concerning clinical definitions and possible sub-forms relating to particular internet applications and/or activities). Future studies are needed to explore valid and reliable outcome measures and, certainly, further randomized controlled trials encompassing long-term follow-up data will be required to evaluate the treatment effects in large samples of "Internet addicted" patients. Research is also needed into whether addicts who use a particular medium/specific form of the Internet require different types of intervention.

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