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Review Article

Psychopharmacology of impulse-control disorders

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CONTENTS

Abstract

Impulse-control disorders are characterized by the failure to resist an impulse or drive to perform an act that may have harmful consequences either to the individual or others. Pathological gambling is the most well recognized and widely studied of the disorders categorized by DSM-IV-TR criteria, in terms of both prevalence and pharmacological treatment. The other disorders categorized by DSM-IV-TR are intermittent explosive disorder, kleptomania, pyromania and trichotillomania. Other less well recognized disorders of impulse control include skin picking, compulsive buying and compulsive computer use. A review of the literature indicates that impulse-control disorders may be relatively common and are likely to be underreported. Individuals diagnosed with an impulse-control disorder are likely to have other other psychiatric co-morbidities, particularly mood, substance use and obsessive-compulsive disorders. A current or lifetime diagnosis of a co-existing psychiatric disorder complicates both the diagnosis and the choice of treatment in an individual with an impulse-control disorder. However, studies published to date have indicated that selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics, opiate antagonists and mood stabilizers may all have a place in the treatment of these disorders. Very few randomized, controlled studies have been performed, however, particularly in the less well recognized impulse-control disorders, and larger studies are required in these heterogeneous populations to determine the efficacy of these therapies.

Introduction

Impulsivity is a core feature of many psychiatric disorders. When not classified according to other DSM-IV-TR criteria, the failure to resist an impulse, drive or temptation to perform an act that is harmful to the individual or to others is the essential feature of Impulse-Control Disorders Not Elsewhere Classified (1, 2). The following disorders are currently included in this section: pathological gambling, trichotillomania, intermittent explosive disorder, kleptomania, pyromania and impulse-control disorder not otherwise specified (NOS). Most of these disorders are characterized by an increasing sense of tension or arousal before committing the act, followed by pleasure, gratification or relief. Individuals may or may not experience regret, self-reproach or guilt (1). In addition to the aforementioned disorders, a number of other disorders related to poor impulse control have also received attention in the professional and lay literature. These include skin picking (which is specifically mentioned in Impulse-Control Disorder NOS in the DSM-IV-TR criteria), compulsive buying and compulsive computer use (2).

Despite data that suggest impulse-control disorders are relatively common and are associated with substantial morbidity and mortality, they have historically received little clinical or research attention (2, 3). Their prevalence is very difficult to establish, and most published studies have evaluated the co-occurrence of impulse-control disorders in patients with other psychiatric diagnoses (4-6). In these studies, between 19% and 38% of patients were diagnosed with at least one co-occurring impulse-control disorder. In a study assessing these disorders in voluntarily hospitalized psychiatric patients (6), only 1.5% of patients had an admission diagnosis of an impulse-control disorder. The high apparent prevalence of impulse-control disorders in patients with other psychiatric disorders must be considered cautiously, as the data were based on subjective reports, and validated diagnostic instruments for these disorders do not exist. However, the findings have significant treatment implications, and for this reason it is important for clinicians and psychiatrists to be able to accurately identify the specific disorders (6).

Pathological gambling

Pathological gambling is an area of increasing interest to researchers, and of all the impulse-control disorders, it

is probably the most widely studied in terms of pharmacological and psychotherapy. It is characterized by persistent and recurrent maladaptive gambling behavior that results in disruption to the life of the individual and his or her family (1). Community studies estimate the lifetime prevalence of pathological gambling to be between 0.4% and 3.4% in adults, and up to one-third of all pathological gamblers are women (1, 2). Prevalence rates are increasing and also tend to be higher in adolescents than in adult populations (7). A study conducted in the Pathological Gambling Unit in Barcelona, Spain, demonstrated that older patients (27 years or more) had higher scores on psychopathology subscales than younger patients (17-26 years), indicating that their gambling behavior had a more detrimental impact on their daily life (8). Results from a U.S. national epidemiological survey on alcohol and related conditions identified almost three-quarters of pathological gamblers as having an alcohol use disorder, and 60% had a personality disorder. The associations between pathological gambling and substance use, mood, anxiety and personality disorders were significant and positive, even after controlling for sociodemographic and socioeconomic characteristics (9). Particular attention has been focused on the co-morbidity of pathological gambling with bipolar spectrum disorders and attention deficit hyperactivity disorder (ADHD), and their influence upon treatment response (10). A number of pharmacological treatments have been investigated for pathological gambling, including selective serotonin reuptake inhibitors (SSRIs), postsynaptic 5-HT antagonists, opiate antagonists and atypical antipsychotics.

The serotonergic system is likely to have a significant role in the etiology of pathological gambling and a number of studies have investigated the efficacy of SSRIs in the disorder. Paroxetine was evaluated in a 16-week, double-blind, placebo-controlled study conducted in 76 patients (mean age 45 years) in the U.S. and Spain. Patients received paroxetine 10-60 mg/day depending on clinical response and tolerability. The primary outcome measure was the Clinical Global Impressions (CGI) scale, and although patients treated with paroxetine consistently demonstrated an advantage over placebo, the differences did not reach statistical signficance. There was a high placebo response rate (49%) in this study that was comparable to the response rate in the paroxetine group (59%) (11). An earlier study by the same group of investigators found statistically significantly greater reductions in the total score of the Gambling Symptom Assessment Scale and significantly greater improvements on the CGI scale at weeks 6 through 8 in the paroxetine group compared with the placebo group. This study was conducted in 45 patients and enrolled patients with a pathological gambling disorder without any other Axis I disorder present (12).

The efficacy of sertraline in the treatment of pathological gambling was evaluated in a double-blind, placebo-controlled pilot study in 66 patients treated for 6 months with 50-150 mg/day. The primary outcome measure was the responder rate with respect to the Criteria for Control of Pathological Gambling Questionnaire (CCPGQ). Response rates of over 70% were observed in both treatment groups and the difference between the groups was not statistically significant (13).

The efficacy and tolerability of the long-acting opioid antagonist nalmefene hydrochloride were evaluated in a 16-week, randomized, double-blind, placebo-controlled study in 207 patients with pathological gambling disorder. Doses of 25, 50 and 100 mg/day were evaluated. The two lower dose groups had significantly improved scores on the Yale-Brown Obsessive Compulsive Scale (YBOCS) Modified for Pathological Gambling (the primary efficacy parameter) compared with placebo. However, doses of 50 and 100 mg/ day were associated with intolerable side effects. This study represents the largest randomized pharmacotherapy trial in patients with a pathological gambling disorder (14).

The anticonvulsant topiramate is a γ-aminobutyric acid (GABA) agonist that attenuates glutamatergic transmission. Pilot studies showed that topiramate might be active in the treatment of specific disorders of impulse control. A randomized, blind-rater study was therefore conducted to compare the efficacy of topiramate *versus* the SSRI fluvoxamine in 31 male patients with pathological gambling disorder. Patients received either topiramate 200 mg/day or fluvoxamine 200 mg/day for 12 weeks. Both drugs were titrated up from 25 mg/day on entry to the maximum dose on day 12. A number of rating scales were administered to the patients, including the CGI-Improvement Scale. Nine of the 12 topiramate completers and 6 of 8 fluvoxamine completers reported full remission of gambling behavior. The number of patients completing the study was lower in the fluvoxamine group. There was an improvement in the CGI-Improvement score in both groups at week 12 compared with baseline; however, this was only significant in the topiramate group (15).

Bupropion is a safe and effective antidepressant. It is a dopamine reuptake inhibitor and is approved by the U.S. Food and Drug Administration (FDA) for the treatment of nicotine dependence. Early data on the use of bupropion in chemical addiction, and evidence that pathological gambling was related to both mood and addictive disorders, led to the investigation of bupropion in the treatment of pathological gambling disorder. A pilot study conducted in 15 patients refractory to treatment in two trials of SSRIs showed that a dose of sustained-release bupropion up to 450 mg/day for 12 weeks resulted in 10 of 12 completers reporting full remission (16). A preliminary, blind-rater study compared sustained-release bupropion *versus* naltrexone in the treatment of pathological gambling (17). The opioid antagonist naltrexone was chosen as comparator following a double-blind, placebo-controlled trial in 83 patients (18) that indicated its potential efficacy in reducing the symptoms of pathological gambling. A total of 36 males with pathological gambling disorder were randomized to receive either bupropion up to 450 mg/day or naltrexone up to 150 mg/day for 12 weeks. Both treatments were similarly effective; in the bupropion group, 9 of 12 completers were rated as full responders compared with 10 of 12 in the naltrexone group (17).

Sustained-release lithium, a mood stabilizer, was evaluated in 40 patients with a pathological gambling disorder concurrent with bipolar spectrum disorders. Gambling severity, mood, anxiety and impulsivity scales were assessed in a 10-week, randomized, double-blind, placebo-controlled treatment study of lithium carbonate titrated to achieve blood levels of 0.6-1.2 mEq/l. There were significant improvements in total pathological gambling scores on the YBOCS, including both thoughts/urges and behavior, and on the CGI-severity of pathological gambling scale. Affective instability was also lower in the group treated with lithium, and gambling severity was significantly correlated with improvement in mania ratings (19).

Drug treatment for pathological gambling is a focus of current research and development, with five sponsored phase II and III clinical trials ongoing (20-25). Studies published to date require cautious interpretation because they have generally been conducted in small numbers of patients over a relatively short period of time. The interpretation of the results has also been affected by the high placebo response in a number of studies, which suggests that patients who seek help and are followed up consistently, as is the case with a clinical trial, are likely to respond positively. The interpretation of results is also complicated by the presence of co-morbid conditions that are likely to affect the response to certain pharmacological interventions. It remains difficult to extrapolate the results of studies because patients with a pathological gambling disorder represent a heterogeneous group with multiple co-morbidities. To overcome some of the limitations of earlier studies, larger studies are under way. These include placebo-controlled phase III studies with naltrexone (20) and nalmefene (21) in 156 and 225 patients respectively, a placebo-controlled study of bupropion in 80 patients (22), and a phase II study evaluating the efficacy of sertraline in patients with a concurrent diagnosis of alcohol dependence (23). In addition, a placebo-controlled phase III study is investigating topiramate in 120 patients (24), and an open phase I study is evaluating the antioxidant *N*-acetylcysteine in 20 patients (25).

Kleptomania

Kleptomania is characterized by the recurrent failure of an individual to resist impulses to steal items even though the items are not needed for their personal use or for their monetary value (1). The thefts are generally not preplanned and do not fully take into account the chances of apprehension. Kleptomania may be associated with compulsive buying and is more prevalent in females. The overall prevalence of kleptomania is unknown, but it probably affects less than 1% of the adult population. Consistent with the classification of impulse-control disorders, kleptomania shows substantial co-morbidity, and mood disorders and obsessive-compulsive personality traits are common in patients diagnosed with kleptomania (2).

There are few controlled clinical trials of pharmacotherapy for kleptomania reported in the literature. The majority of reports are open studies, case series or case reports. These have indicated a role for SSRIs, naltrexone and topiramate in the treatment of kleptomania. A chart review was conducted of 17 consecutive adult outpatients who had sought treatment for kleptomania and were treated with naltrexone as monotherapy. Approximately one-third of the patients had a concurrent affective disorder, and a further 2 patients had a concurrent anxiety disorder. Patients were treated with up to 200 mg naltrexone daily, with a mean effective dose of 135 mg/day. Patients were followed up for up to 3 years, and at the last visit three-quarters of the patients (13/17) reported a reduction in their urges to steal, and 41% reported no stealing behavior. In addition, the mean CGI score decreased significantly (26).

A randomized, double-blind, placebo-controlled trial of the SSRI escitalopram is ongoing in 24 adult patients with kleptomania of at least 1 year's duration, without concurrent antisocial personality disorder, psychotic disorders, bipolar affective disorder or alcohol or substance abuse. An initial 7-week open treatment period with escitalopram up to 20 mg/day identified responders who then entered a 4-month double-blind treatment period with either escitalopram or placebo. Of 22 patients who completed the open-label phase, 18 responded to therapy, defined as a reduction of at least 50% in the baseline frequency of theft episodes and a CGI-Improvement score of "much improved" or "very much improved". Fourteen patients entered the double-blind phase of the study, 5 of whom subsequently relapsed. Preliminary evidence from the open phase of the study suggests that escitalopram may demonstrate efficacy in the treatment of kleptomania (27).

Intermittent explosive disorder

Intermittent explosive disorder is the occurrence of discrete episodes of failure to resist aggressive impulses that result in serious assault or destruction of property. The degree of aggressiveness exhibited is grossly out of proportion to any precipitating factors. The aggressive episodes may be preceded by symptoms such as tingling, tremor and palpitations (1). Despite the fact that intermittent explosive disorder is categorized as an impulse-control disorder by the American Psychiatric Association, many physicians remain skeptical about its existence as a discrete syndrome that is not explained by another Axis I or II disorder (2). However, in recent years it has come under the spotlight because of its association with "road rage". Early reports indicated a prevalence of intermittent explosive disorder of less than 2% in psychiatric patients or in self-referred aggressive subjects (28). A recent study aimed to characterize the clinical epidemiology of the disorder by analyzing data from a large private psychiatric outpatient practice set in Rhode Island Hospital, U.S.A. Data from 1,300 patients indicated that 6.3% met criteria for a lifetime diagnosis of intermittent

explosive disorder, and about half of these subjects met criteria for a concurrent diagnosis. Intermittent explosive disorder was the principal diagnosis in only 0.6% of patients. There was substantial co-morbidity within the group of patients with a lifetime diagnosis; concurrent lifetime diagnoses included mood disorder (76%), anxiety disorder (78%) and alcohol/drug use disorder (60%). Alcohol and/or drug use disorders were nearly 40% more frequent in patients diagnosed with intermittent explosive disorder than in those without that diagnosis. The peak age of onset was in the teenage years, especially in male patients. It occurred earlier than almost all co-morbid disorders, suggesting that its development may be independent of most other disorders (28).

A pilot study was performed in 25 subjects meeting DSM-IV criteria for either cluster B personality disorder or intermittent explosive disorder. Subjects received 20 mg/day of the SSRI citalopram, with titration up to 60 mg/day by week 4 depending on tolerability. Treatment continued for a further 4 weeks. The primary outcome measure was the Overt Aggression Scale-Modified (OAS-M) and statistically significant decreases from baseline were observed. The study provided preliminary support for treatment with citalopram in reducing impulsive aggressive behavior (29).

The efficacy of the antiepileptic agent divalproex sodium in the treatment of patients with pervasive developmental disorder and intermittent explosive disorder was assessed by a retrospective chart review of 300 patients. Medical records were reviewed for patients admitted to a specialized unit for the management of adults with developmental disabilities. Over a 1-year period, 203 patients meeting diagnostic criteria for intermittent explosive disorder and mental retardation were identified, 108 of whom received divalproex as monotherapy or adjunctive therapy. A total of 71% of patients were improved or much improved based on CGI or Global Assessment of Functioning (GAF) scores (30). Divalproex is being evaluated in comparison with fluoxetine in a randomized, double-blind, placebo-controlled phase II study in 144 patients with a diagnosis of intermittent explosive disorder. Patients with current alcohol or drug abuse or dependence are excluded (31).

The efficacy, tolerability and safety of the antiepileptic levetiracetam were assessed retrospectively in 100 children, adolescents and adults with aggression evident as oppositional defiant disorder, conduct disorder, intermittent explosive disorder and impulse-control disorder. The mean dose of levetiracetam was 1540 mg/day. Efficacy as assessed by symptom severity on a Likert scale was good in 45% of patients and partial in a further 15% (32).

In a pilot study examining the effects of bupropion and escitalopram, 13 patients diagnosed with a cluster B personality disorder or intermittent explosive disorder were treated with open-label bupropion (300-400 mg/day) or escitalopram (10-20 mg/day) for 10 weeks. Continuous performance laboratory measures of impulsivity and overt aggressive scores of the OAS-M were reduced in both treatment groups (33).

Pyromania

The essential feature of pyromania is the presence of multiple episodes of deliberate and purposeful fire setting by an individual who has a fascination with, or attraction to, fire and its situational contexts (1). The fire setting is not an expression of sociopolitical ideology, nor of anger or vengeance; it is not carried out for secondary gain. Pyromania is apparently rare, but does occur much more frequently in males, especially those with poorer social skills and learning difficulties.

There are no published or ongoing studies specifically evaluating pharmacological treatment of pyromania.

Compulsive buying

Compulsive buying is not categorized specifically as an impulse-control disorder. However, it is now widely considered as an example of the disorder, and can thus be included under the residual category Impulse-Control Disorder NOS. Compulsive buying is characterized by persistent or poorly controlled preoccupations, urges or behaviors with regard to shopping or spending that lead to adverse consequences. It is strongly correlated with associated Axis I and II disorders such as eating, mood and anxiety disorders, as well as obsessive-compulsive and personality disorders (2). The consequences of compulsive buying include personal, social and occupational disruption, and frequently debt. The disorder manifests itself mainly with respect to personal consumer goods and not with everyday household shopping (34).

Although a description of compulsive buying was made as early as 1915, it has only emerged as a widespread phenomenon since the early 1990s. The prevalence of compulsive buying has not been established in an epidemiological study, but estimates as high as 16% have been made. Conservative estimates indicate that 2-5% of the population may have the disorder. The disorder predominantly affects women, who represent between 74% and 93% of compulsive buyers, and younger people are more prone to the disorder (34). In three questionnaire studies performed in the U.K. that included adults who had contacted a compulsive buying self-help organization, age and gender differences were confirmed and materialistic value endorsement also emerged as the strongest predictor of a compulsive buying tendency (34). In a population of 204 consecutively admitted psychiatric inpatients (6), compulsive buying was the most common current impulse-control disorder, occurring in 9% of the sample.

Pharmacotherapy for the treatment of compulsive buying has included SSRIs and naltrexone. Antidepressants and mood stabilizers have also been effective in patients with co-morbid depression or mood disorders (35). Citalopram was evaluated in a 7-week open-label trial followed by a 9-week, double-blind, placebo-controlled discontinuation trial. A total of 24 subjects diagnosed with a compulsive buying disorder were enrolled. Subjects with obsessive-compulsive disorder, bipolar disorder, substance abuse or dependence, or psychotic disorders were

excluded. Citalopram was initiated at a dose of 20 mg/day and increased to a maximum of 60 mg/day depending on response and tolerability. Fifteen subjects (63%) met the "response" criteria at week 7, defined as achieving at least a 50% decrease on the YBOCS-Shopping Version and rated as "much improved" or "very much improved" on the CGI-Improvement scale. Of the 15 subjects who entered the double-blind phase, 5 of 8 randomized to placebo subsequently relapsed, compared with none of the 7 subjects who received citalopram ($p = 0.019$) (36).

Citalopram was also evaluated in an earlier 12-week open-label study in 24 subjects with a compulsive buying disorder, excluding those with obsessive-compulsive disorder, bipolar disorder, substance abuse or dependence, or psychotic disorders. Citalopram 20-60 mg/day resulted in rapid and sustained improvements on both the YBOCS-Shopping Version and the CGI-Improvement scale (37). Seventeen of 24 subjects (71%) were responders and were followed up by telephone interview 3, 6, 9 and 12 months after study completion. At each of these time points, over 70% of responders were in remission, and at 12 months the median debt had decreased from USD 20,000 to USD 14,000 (38).

Escitalopram was also evaluated in an open-label study followed by double-blind discontinuation. Adults diagnosed with a compulsive buying disorder for at least 1 year and engaging in compulsive buying at least weekly for the previous 3 months received 10-20 mg of escitalopram for 7 weeks depending on response and tolerability. Subjects with obsessive-compulsive disorder, bipolar disorder, substance abuse or dependence, or psychotic disorders were excluded. "Responders" (see 36) were randomized to receive escitalopram or placebo for a further 9 weeks. Preliminary results were presented when 11 of a planned 24 subjects had been enrolled. Ten subjects (all women; mean age 47 years) completed the open-label phase, 6 of whom were defined as responders. Three of these subjects subsequently relapsed during the double-blind discontinuation phase (39).

Trichotillomania

Trichotillomania is characterized by the recurrent pulling out of one's own hair that results in noticeable hair loss. The most common sites affected are the scalp, eyebrows and eyelashes. The disturbance must cause significant distress or impairment in social, occupational or other areas of functioning. Other habits such as nail biting, scratching and gnawing are often associated with trichotillomania, and individuals may have concurrent mood, anxiety, substance use, eating or personality disorders (1). The mean age of onset of trichotillomania is prepubertal or early adolescence, and in children the disorder tends to affect both genders equally. In adults, the disorder is much more common among females than males. The prevalence of trichotillomania is probably underestimated due to the secretiveness that is characteristic of the disorder; an anonymous survey of college students found a lifetime prevalence of 0.6% (1, 40).

A recent article in the *British Medical Journal* suggested the possibility of a defect in the Homeo box-containing (*Hox*) genes in patients with trichotillomania, because of its parallel with "barbering" in laboratory mice. The *Hox* genes are involved in hair formation in adult mice, and mice homozygous for a loss of function mutation in the *Hoxb8* gene show excessive pathological grooming. A formal study is required to investigate this interesting possibility (41).

Published reports of pharmacotherapy for trichotillomania have included case reports and case series showing positive benefit in the treatment of the disorder for bupropion (42), escitalopram (43, 44), topiramate (44), the 5-HT/dopamine antagonist olanzapine (45) and the atypical antipsychotic quetiapine (46). Escitalopram (10-30 mg/ day for 12 weeks) has also been investigated in an open-label study in 20 patients with trichotillomania. Of 12 patients who completed the study, 8 were responders, defined as "very much improved" or "much improved" on the CGI-Improvement scale and at least a 50% decrease in symptoms as assessed by the Trichotillomania Severity Scale. Improvement in co-morbid depressive and anxiety symptoms was observed (47).

An open-label study of olanzapine was conducted in 18 patients with trichotillomania without co-morbid psychiatric disorders. Olanzapine was titrated to a maximum dose of 10 mg/day for 3 months. In an intention-to-treat analysis, hair pulling as measured by the Massachusetts General Hospital Hairpulling scale (MGHHS) decreased by 66% from baseline, and mean scores on the Hamilton Rating Scale for Anxiety (HAM-A) decreased by 63%. There was also a significant improvement on the CGI-Improvement scale, and 4 patients achieved complete remission at the end of the study period (48). A randomized, double-blind, placebo-controlled phase III trial of olanzapine is currently ongoing. The study aims to recruit 34 patients with trichotillomania, but excluding patients with any other Axis I primary diagnosis or co-morbid obsessive-compulsive disorder, or alcohol or substance abuse (49).

In a randomized, waiting list-controlled study, the efficacy of fluoxetine hydrochloride and behavioral therapy was compared in 43 patients with trichotillomania. This study showed that behavioral therapy was highly effective in the short-term treatment of trichotillomania. Fluoxetine was ineffective in reducing symptoms; in fact, gain scores for the MGHHS-actual-pulling subscale were significantly larger in the waiting list group than in the fluoxetine group (50).

Skin picking

Skin picking, although not recognized as a unique subcategory of the impulse-control disorders, is specifically mentioned under Impulse-Control Disorder NOS (1). It is a self-injurious behavior that can result in severe tissue damage. High prevalence rates for pathological skin picking have been reported, varying from 2% in dermatology patients to 2-4% in a student population. As with other impulse-control disorders, high rates of psychiatric

co-morbidities have been documented, and subjects report significantly greater social anxiety, embarrassment and avoidance compared with controls. In addition, repetitive skin picking has been reported to have a negative impact on quality-of-life indices, including leisure and athletic activities, clothing choice and sexual activity (51).

In a sample of 31 subjects engaging in severe self-injurious skin picking, the mean age at onset was 15 years and the mean duration of the illness was 21 years. Twenty-seven (87%) of the subjects were female. Co-morbidities were common, with 48% of subjects meeting criteria for at least one mood disorder and 65% for at least one anxiety disorder. Obsessive-compulsive disorder was diagnosed in approximately 50% of the sample, and alcohol abuse or dependence was common (39%). In this study, subjects were recruited through bulletin board notices at Massachusetts General Hospital (MGH), newspaper advertisements and clinician referrals (52).

Very few reports exist of pharmacotherapy in the treatment of repetitive skin picking. Escitalopram was investigated in an 18-week open-label study in 15 adult subjects with self-injurious skin picking for at least 6 months. Subjects with co-morbid psychiatric conditions, including obsessive-compulsive disorder and a history of substance dependence, were excluded. Following a 2-week single-blind placebo treatment, patients received escitalopram 10 mg/day, increasing to 30 mg/day or the maximum tolerated dose. In a preliminary analysis of 10 study completers, significant improvements were observed in MGH Skin Picking Scale scores, CGI-Improvement scores, Skin Picking Treatment Scale and Skin Picking Impact Scale. Improvements in quality-of-life assessments were also observed (53).

Compulsive computer use

Compulsive computer use has been described in the literature as “internet addiction”, and is characterized by a preoccupation with computer usage that is overly time-consuming, causes personal distress and has the potential to cause serious psychosocial consequences such as occupational or financial difficulties (2, 54). It has been described as a disorder of impulse control, and as such may be classified according to DSM-IV-TR criteria under Impulse-Control Disorder NOS. Indeed, classification and diagnostic criteria for problematic internet use have been proposed, describing it as a maladaptive preoccupation with internet use (55). In making this classification, the authors have proposed that at least one of the following criteria must be satisfied: a preoccupation with use of the internet that is experienced as irresistible, or excessive use of the internet for periods of time longer than planned.

It has been estimated that as many as 5-10% of internet users have an internet addiction, although no formal surveys have been conducted (2). In an evaluation of 20 individuals with problematic internet use, all met DSM-IV criteria for an impulse-control disorder NOS. All 20 subjects had at least one lifetime Axis I diagnosis in addition to their problematic internet use, and 14 had a lifetime diagnosis of bipolar disorder (53). A web-based questionnaire adapted from DSM-IV criteria for gambling and alcohol addiction was used to evaluate internet addiction on two separate occasions in 2000 and 2005. The questionnaire was anonymously completed by 606 and 239 people in 2000 and 2005, respectively. Their total internet addiction scores (TIAS) were calculated. Mean scores were similar in both years and were inversely related with age and income. Being a student, housewife or unemployed predicted a higher TIAS (56).

The prevalence of internet addiction and the relationship between internet addiction and depression, impulsivity and obsessive-compulsive behavior were evaluated by questionnaire in 1,408 Korean high school students. The prevalence of internet addiction was 4% as assessed by the Young Internet Addiction Scale. This group had significantly higher mean scores for depression and impulsivity measured by the Beck Depression Inventory and the Barratt Impulsiveness Scale, respectively. They also had significantly higher mean scores for obsessive-compulsive behavior assessed by the Maudsley Obsessive-Compulsive inventory (57).

There have been no formal studies of pharmacotherapy for compulsive computer use.

Completed and ongoing studies of experimental therapies for impulse-control disorders are summarized in Tables I and II, respectively.

Table I: Completed studies of experimental therapies for impulse-control disorders (continuously updated information available in Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Pathological gambling	Multicenter, Randomized, Double-blind, Placebo-controlled	Paroxetine, 10-60 mg/d Placebo	76	Paroxetine- and placebo-treated groups showed comparable overall improvement in patients with pathological gambling	11
	Randomized, Double-blind, Placebo-controlled	Paroxetine, 20 mg/d x 2 wks → 20-60 mg/d [titrated by 10 mg/wk] x 6 wks Placebo	45	Paroxetine was more effective than placebo, showing positive effects from week 6 of therapy at doses generally greater than 40 mg/d	12

Continuation

Table I (cont.): Completed studies of experimental therapies for impulse-control disorders (continuously updated information available in Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Pathological gambling	Randomized, Double-blind, Placebo-controlled	Sertraline, 100 mg/d p.o. [titrated from 50 mg/d over 4 wks, and increased to 150 mg if tolerated and no response @ wk 8] x 24 wks Placebo	66	Sertraline was not superior to placebo in the treatment of pathological gambling, although the small sample size and the high response to placebo limited the power of the study	13
	Multicenter, Randomized, Double-blind, Dose-finding, Placebo-controlled	Nalmefene, 25 mg/d x 16 wks Nalmefene, 50 mg/d x 16 wks Nalmefene, 100 mg/d x 16 wks Placebo	207	Nalmefene showed potential as a treatment for pathological gambling; tolerability was limited with the higher doses	14
	Comparative, Randomized	Topiramate, 25-200 mg/d x 12 wks [titrated to 50 mg on d 3 → 50 mg 1x/3 d] Fluvoxamine, 25-200 mg/d x 12 mg [titrated to 50 mg on d 3 → 50 mg 1x/3 d]	31	Topiramate and fluvoxamine could be used to treat male patients with pathological gambling; topiramate was well tolerated and associated with higher complete remission rates	15
	Open, Comparative, Randomized	Bupropion-SR, 150 mg/d x 1 wk → 150 mg b.i.d x 2 wks → 300-450 mg/d x 9 wks Naltrexone, 25 mg/d x 4 d → 50 mg b.i.d. x 10 d → 100-150 mg x 9 wks	36	Sustained-release bupropion may be as effective as naltrexone in the treatment of pathological gambling	17
	Randomized, Double-blind, Placebo-controlled	Lithium, 300 mg p.o. o.d. [P.M.] x 4 d → 300 mg p.o. [A.M.] + 300 mg [P.M.] x 4 d → 300 mg p.o. [A.M.] + 600 mg [P.M.] x 6 d → Cmin 0.6-1.2 mEq/l x 8 wks Placebo	40	Sustained-release lithium may be an effective treatment for reducing gambling behavior and affective instability in pathological gamblers	19
Kleptomania	Open	Naltrexone, 50-200 mg/d [titrated by 50 mg/d 1x/2 wks]	17	Naltrexone effectively reduced the urge to steal and stealing behavior in patients with kleptomania	26
	Randomized, Double-blind, Placebo-controlled	Escitalopram, 10 mg/d x 4 wks → 20 mg/d x 3 wks → 20 mg/d x 4 mo Escitalopram, 10 mg/d x 4 wks → 20 mg/d x 3 wks → Placebo x 4 mo	24	Escitalopram was effective in reducing the frequency of theft episodes in patients with kleptomania	27
Intermittent explosive disorder	Open	Citalopram, up to 60 mg p.o. o.d. [titrated from 20 mg/d over 4 wks in weekly increments as tolerated] x 8 wks	25	Citalopram effectively reduced impulsive aggressive behavior	29
	Retrospective	Valproate semisodium	108	Valproate semisodium as monotherapy or add-on therapy improved agitation and mood lability in patients with intermittent explosive disorder and mental retardation	30
	Open	Levetiracetam, 1540 [mean] mg o.d. x 1 [max.] y	100	Levetiracetam was safe and effective in patients with aggressive disorders	32
	Open, Comparative	Bupropion, 300-400 mg/d x 10 wks Escitalopram, 10-20 mg/d x 10 wks	13	Bupropion and escitalopram similarly decreased both laboratory and clinical measures of impulsive behavior in subjects with intermittent impulsive behavior	33
Compulsive buying	Randomized, Double-blind, Placebo-controlled	Citalopram, 20-60 mg/d [titrated 1x/2 wks] x 7 wks → [if response] 60 mg x 9 wks Citalopram, 20-60 mg/d [titrated 1x/2 wks] x 7 wks → [if response] Placebo	24	Citalopram appeared to be a safe and effective treatment for compulsive shopping	36
	Open	Citalopram, 20-60 mg/d x 12 wks	24	Citalopram showed response in 71% of compulsive buyers; 12 months after study end, 73% of responders were still in remission	37, 38

Continuation

Table I (cont.): Completed studies of experimental therapies for impulse-control disorders (continuously updated information available in Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
	Randomized, Double-blind, Placebo-controlled	Escitalopram, 10-20 mg/d 7 wks → [if response] Escitalopram x 9 wks	11	Escitalopram was well tolerated and had therapeutic efficacy in the treatment of compulsive buying	39
Trichotillomania	Open	Escitalopram, 10-30 mg/d x 12 wks	20	Escitalopram treatment for 12 weeks led to significant inprovement in trichotillomania in some patients	47
	Open	Olanzapine, 10 [max.] mg/d x 3 mo	18	Olanzapine showed efficacy as monotherapy in patients with trichotillomania	48
	Open, Randomized	Fluoxetine, 60 mg x 12 wks (n=11) Behavioral therapy x 12 wks (n=14) Control (n=15)	43	Behavioral therapy was highly effective for reducing symptoms of trichotillomania in the short term; fluoxetine had no benefit	50
Skin picking	Open	Escitalopram, 10-30 mg/d x 18 wks	15	Escitalopram provided significant reductions in skin picking urges and behavior and improved quality of life of patients with this obsessive-compulsive disorder	53

Table II: Ongoing studies of experimental therapies for impulse-control disorders (continuously updated information available in Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Pathological gambling	Randomized, Double-blind, Placebo-controlled	Naltrexone x 16 wks Placebo x 16 wks	156	The study will establish the best dose of naltrexone for treating patients with pathological gambling with severe urge symptoms	20
	Multicenter, Randomized, Double-blind, Placebo-controlled	Nalmefene Placebo	225	This study will determine whether nalmefene is safe and effective in the treatment of pathological gambling	21
	Randomized, Double-blind, Placebo-controlled	Bupropion x 12 wks Placebo x 12 wks	80	This study will determine whether bupropion is an effective treatment for pathological gambling	22
	Randomized, Double-blind, Placebo-controlled	Sertraline, 25 mg o.d. [A.M.] + Relapse prevention therapy x 1 wk → [if no improvement] → 50 mg o.d. [A.M.] x 1 wk → 50-200 mg/d x 8 wks	30	This study will determine the efficacy of sertraline in combination with relapse prevention therapy in gamblers with a diagnosis of alcohol dependence	23
	Randomized, Double-blind, Placebo-controlled	Topiramate, 50-300 mg x 14 wks [titrated over 6 wks] → [tapered over 1 wk] Placebo Placebo + Relapse prevention therapy	120	This study will assess the efficacy of topiramate in the treatment of pathological gambling	24
	Open	Acetylcysteine, 600 mg/d x 2 wks →1200 mg/d →1800 mg/d	20	This study will assess the efficacy of acetylcysteine in the treatment of pathological gambling	25
Intermittent explosive disorder	Randomized, Double-blind, Placebo-controlled	Fluoxetine x 12 wks	144	The study will compare fluoxetine *versus* valproate as a treatment for aggressive behavior in individuals with intermittent explosive disorder	31
Trichotillomania	Randomized, Double-blind, Placebo-controlled	Olanzapine x 12 wks	34	This study will assess the efficacy and safety of olanzapine in trichotillomania	

Conclusions

Pharmacotherapy for impulse-control disorders is complicated by the frequent diagnosis of a co-existing psychiatric disorder in these patients. However, studies published to date have indicated that SSRIs, atypical antipsychotics, opiate antagonists and mood stabilizers may be effective in the treatment of these disorders. Very few randomized, controlled studies have been performed, however, particularly in the less well recognized impulse-control disorders, and larger studies are required in these heterogeneous populations to evaluate the efficacy of these therapies.

Impulse-control disorders in patent literature

A review of the patent literature provides an indication of R&D trends in this area. A clear increase in patent claims for impulse-control disorders can be seen from 2002 on, with 2005 being the most productive year yet, particularly for combination therapies incorporating drugs currently available for other disorders (see Appendix I and Fig. 1, p. 255-258). A continuous update on future trends from patent line extensions can be obtained from Prous Science Integrity®.

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Appendix I: Treatments for impulse-control disorders in patent literature, ordered by publication date (continuously updated information available in Prous Science Integrity®).

Selected products	Treatment	Mechanism	Patent* number	Publication date	Applicant
Clomipramine	Trichotillomania Onchyphagia		US 5008262	16.04.91	Dept. Health Human Serv.
Clomipramine Fluoxetine Fluvoxamine	Trichotillomania Onchyphagia	Serotonin reuptake inhibitor	WO 1992018005	29.10.92	Natl. Inst. Health
239203 [I]	Trichotillomania	5-HT1A receptor antagonist	US 5614523	25.03.97	Eli Lilly
Naltrexone Naloxone Nalmefene Levallorphan	Various ICDs	Opioid receptor antagonist	US 5780479	14.07.98	Regents Univ. Minnesota
Ecopipam	Pathological gambling	Dopamine D1,D5 receptor antagonist	WO 1999044615	10.09.99	Schering
Topiramate	Various ICDs		WO 2000050020	31.08.00	Univ. Cincinnati
MPEP	Pathological gambling	mgluR5 antagonist	WO 2001066113	13.09.01	Glaxo
257955 [II]	Various ICDs	Selective estrogen receptor modulator	WO 2002003975	17.01.02	American Home
CP-293019	Pathological gambling	Dopamine D4 receptor ligand	EP 1177792	06.02.02	Pfizer
Topiramate	Various ICDs		WO 2002043731	06.06.02	Univ. Florida
Ecopipam	Pathological gambling	Dopamine D1,D5 receptor antagonist	US 6410527	25.06.02	Schering
YKP-509	Trichotillomania Pathological gambling Kleptomania		WO 2002067923	06.09.02	Ortho-McNeil
Escitalopram	Various ICDs	Serotonin reuptake inhibitor	WO 2002087566	07.11.02	Lundbeck
329250 [III]	Trichotillomania	Serotonin reuptake inhibitor/5-HT1A receptor antagonist	WO 2002088136	07.11.02	Wyeth
Femoxetine Citalopram Nefazodone Fluvoxamine Imipramine Clomipramine Venlafaxine Paroxetine Fluoxetine Duloxetine Dapoxetine Sertraline Vilazodone Escitalopram	Various ICDs	Serotonin reuptake inhibitor	WO 2004000326	31.12.03	Lundbeck
in combination with					
CGP-36742 CGP-35348 CGP-54626		GABA(B) receptor antagonist			

Continuation

Appendix I (cont.): Treatments for impulse-control disorders in patent literature, ordered by publication date (continuously updated information available in Prous Science Integrity®).

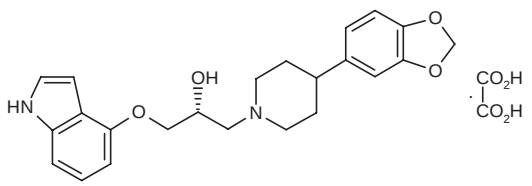
Selected products	Treatment	Mechanism	Patent* number	Publication date	Applicant
CGP-52432 CGP-55845A CGP-71982 CGP-62349 CGP-76290A CGP-76291 GAS-360 Sch-50911					
Femoxetine Citalopram Nefazodone Fluvoxamine Imipramine Clomipramine Venlafaxine Paroxetine Fluoxetine Duloxetine Dapoxetine Sertraline Vilazodone Escitalopram	Various ICDs	Serotonin reuptake inhibitor	WO 2004000326	31.12.03	Lundbeck
in combination with					
CGP-36742 CGP-35348 CGP-54626 CGP-52432 CGP-55845A CGP-71982 CGP-62349 CGP-76290A CGP-76291 GAS-360 Sch-50911		GABA(B) receptor antagonist			
365152 [IV]	Trichotillomania	Drug acting on acetylcholine receptors (nicotine)/ Drug acting on monoamine transporters	WO 2004016608	26.02.04	NeuroSearch
422169 [V]	Various ICDs	Serotonin reuptake inhibitior/Dopamine D4 receptor antagonist	WO 2004020437	11.03.04	Lundbeck
380596 [VI]	Trichotillomania	Dopamine, norepinephrine, serotonin reuptake inhibitor	WO 2004072071	26.08.04	NeuroSearch
Aciclovir** Ganciclovir Famciclovir Azidothymidine	Kleptomania		EP 615750	21.09.04	Scotia Holdings
Botulinum toxin type A	Various ICDs		WO 2004096269	11.11.04	Allergan
422177 [VII]	Trichotillomania	Dopamine, norepinephrine, serotonin reuptake inhibitor	WO 2004113334	29.12.04	NeuroSearch

Continuation

Appendix I (cont.): Treatments for impulse-control disorders in patent literature, ordered by publication date (continuously updated information available in Prous Science Integrity®).

Selected products	Treatment	Mechanism	Patent* number	Publication date	Applicant
422188 [VIII]	Pathological gambling	Cannabinoid CB1 antagonist	WO 2005018645	03.03.05	Pfizer
in combination with					
385757 [IX]		Opioid receptor antagonist			
Gabapentin Pregabalin	Pathological gambling	$\alpha 2$-δ Ligand	WO 2005018670	03.03.05	Pfizer
in combination with					
339630 [X]		Opioid receptor antagonist			
Citalopram	Various ICDs	Serotonin reuptake inhibitor	WO 2005018676	03.03.05	Lundbeck
in combination with					
ALX-5407		Glycine transporter type 1 inhibitor			
Fluvoxamine Fluoxetine Sertraline	Trichotillomania Kleptomania	Serotonin reuptake inhibitor	WO 2005051488	09.06.05	Pfizer
in combination with					
Sumanirole		Dopamine D2 receptor agonist			
Citalopram	Various ICDs	Serotonin reuptake inhibitor	WO 2005056056	23.06.05	Lundbeck
in combination with					
Thioperamide Ciprofixan GT-2394		Histamine H3 receptor antagonist, inverse agonist or partial agonist			
Atomoxetine Reboxetine	Various ICDs	Norepinephrine reuptake Inhibitor	WO 2005060949	07.07.05	Eli Lilly
411952 [XI]	Various ICDs	Cannabinoid CB1 antagonist	US 2005171179	04.08.05	Solvay
Gabapentin Pregabalin	Trichotillomania Kleptomania	GABA modulator	WO 2005082372	09.09.05	Pfizer
in combination with					
266807 [XII]		5-HT1B receptor antagonist			
Azamianserin Amisulpride Olanzapine	Trichotillomania Kleptomania		WO 2005107808	17.11.05	Pfizer

*Other conditions apart from impulse-control disorders are also claimed in these patents. **Patent includes other conditions where a herpesvirus (HSV) is a causative agent.



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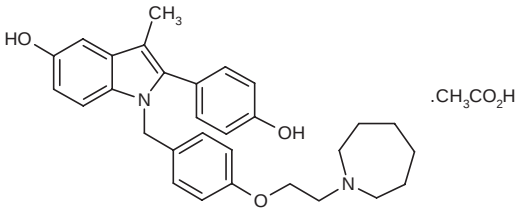

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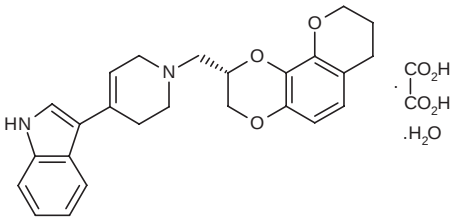

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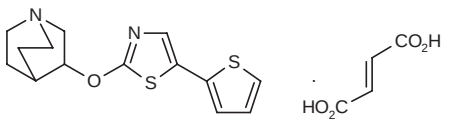

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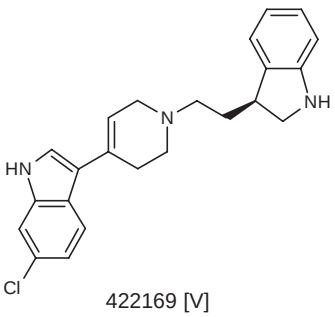

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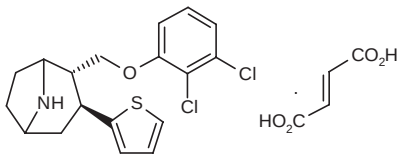

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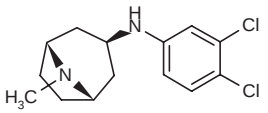

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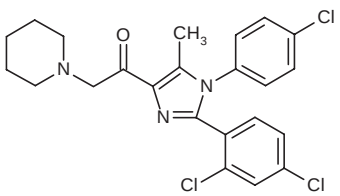

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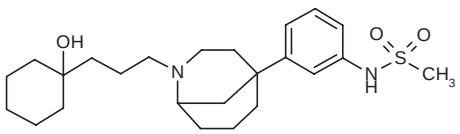

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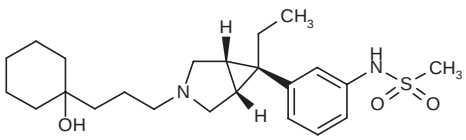

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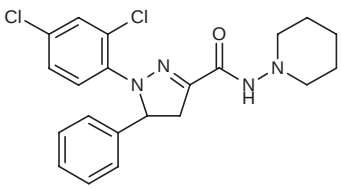
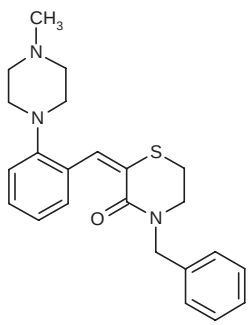


411952 [XI]



266807 [XII]

Fig. 1. Chemical structures of compounds in Appendix I without generic/code name (Entry number [EN] from Prous Science Integrity®).