120

PATHOLOGIC GAMBLING AND IMPULSE CONTROL DISORDERS

MARK N. POTENZA
ERIC HOLLANDER

Impaired regulation of impulse is a central feature in several psychiatric disorders and behaviors, including drug use disorders, cluster B personality disorders such as borderline personality disorder, bipolar disorders, and suicide attempts. The DSM-IV's "impulse control disorders (ICDs) not specified elsewhere" (1) have historically received less attention than other psychiatric conditions. This heterogeneous group of illnesses includes intermittent explosive disorder, kleptomania, pyromania, pathologic gambling (PG), trichotillomania, and ICDs not otherwise specified. We review the neurobiology and treatment of one of these ICDs, PG, and describe the nature and treatments of several other potentially related conditions that have recently received increased attention: (a) compulsive buying (CB); (b) compulsive sexual behavior (CSB); and (c) compulsive computer use (CCU). These disorders, linked by a failure to resist urges to engage in ultimately self-destructive behaviors, appear to be relatively common, frequently go unrecognized for considerable periods, and may constitute greater threats to personal health than is often appreciated.

PATHOLOGIC GAMBLING

Descriptions of gambling and gambling disorders are found in some of the earliest human records (2,3). Historically, gambling has been viewed as a sin and later as a vice (2–5). More recently, disordered gambling has been seen as an illness determined by genetic and environmental factors and individual decision making. The most extreme form of disordered gambling, PG, was first included in the DSM in 1980 (1). Since that time, there has been increasing research into the clinical features and neurobiological causes of PG.

Mark N. Potenza: Director, Problem Gambling Clinic; Department of Psychiatry, Yale University School of Medicine and Connecticut Mental Health Center, New Haven, Connecticut.

Eric Hollander: Professor of Psychiatry, Seaver Autism Research Center, Department of Psychiatry, Mount Sinai School of Medicine, New York, New York.

Theoretic Conceptualizations

PG has been described as sharing features with several groups of disorders (Fig. 120.1). Some authors have hypothesized that PG lies along a compulsive-impulsive spectrum (6,7), and PG represents an obsessive-compulsive (OC) spectrum disorder (8–10). Consistent with the classification of PG as an OC-spectrum disorder, individuals with PG engage in repetitive (gambling-related) behaviors, often in response to overwhelming thoughts to engage in the behavior (11). Studies of comorbidity between OC disorder (OCD) and PG have yielded mixed results, with some studies finding rates of OCD in individuals with PG higher than in the general population (12,13), whereas others have not found elevated rates of comorbidity (14–17) or elevated rates of positive family histories for PG in patients with OCD (18). A direct investigation into OC characteristics of individuals with PG found that those with PG scored significantly higher than those without on the Padua Inventory (19). The differences clustered within two factors corresponding to obsessive qualities of impaired control over mental activity and worries of losing control over motor behavior, respectively (19). Although the findings support the notion that PG lies toward the impulsive end of a compulsive-impulsive spectrum, the authors cite a central difference between gambling in PG and repetitive behaviors in OCD (19). Namely, gambling and actions in other ICDs are often related as pleasurable or egosyntonic, whereas performance of repetitive activities in OCD is generally described as egodystonic. Although one study reported the possibility of the association of PG and OCD with the Huntington disease mutation in a family with PG, OCD, and Huntington disease (20), the neurobiological similarities and differences between PG and OCD remain to be defined more clearly, to explore their relatedness further.

Researchers and clinicians have also described PG as an addiction and have cited similarities to substance use disorders (21–23). In fact, the diagnostic criteria for PG were modeled after those for substance dependence (1) and in-

FIGURE 120.1. Proposed conceptual model for relationships between pathologic gambling (PG) and other psychiatric conditions. ADHD, attention-deficit/hyperactivity disorder.

clude aspects of tolerance, withdrawal, and failed attempts to control the destructive behavior. High rates of comorbidity are observed between PG and substance use disorders. Individuals with PG have high rates of substance use disorders, with rates of nicotine dependence approaching 70% (24), alcohol abuse or dependence in the range of 45% to 55% (12,25), and other drug use problems nearing 40% (26). Conversely, individuals with substance use disorders are four- to tenfold more likely to have PG (27): 9% of opiate addicts in methadone maintenance (28), 17% of alcohol abusers (29), and 15% of cocaine addicts (30) have PG. The high rates of comorbidity have implications with regard not only to potential similarities in the underlying neurobiological bases of PG and substance use disorders, but also to the clinical needs of individuals with PG. Specifically, individuals dually diagnosed with a substance use disorder and PG were found to require more psychiatric admissions and detoxifications than individuals with a substance use disorder without PG (31). A separate study found that individuals with comorbid substance use disorders and PG were at greater risk for contemplated and attempted suicide than individuals with either diagnosis alone (32). These and other findings (33,34) indicate that dually diagnosed individuals with PG appear to be more severely ill than those with either illness alone. Taken together with emerging data suggesting neurobiological similarities between substance use disorders and PG (see the later discussions of genetics and neuroimaging), there is mounting evidence supporting the notion of substance use disorders and PG lying along an addiction spectrum.

High rates of other psychiatric disorders, particularly mood, attention-deficit, and antisocial personality disorders, have also been described in individuals with PG (24, 35–37). Some data suggest that individuals with features of some of these disorders (e.g., cycling mood disorders) could benefit from different treatment interventions (see the later discussion on pharmacotherapy). Further studies are warranted to investigate the precise relationships between these disorders and PG.

TABLE 120.1. PROPOSED ROLES FOR NEUROTRANSMITTER SYSTEMS IMPLICATED IN THE PATHOPHYSIOLOGY OF PATHOLOGIC GAMBLING

Neurotransmitter	Proposed Role
Norepinephrine	Arousal, excitement
Serotonin	Behavioral initiation and cessation
Dopamine	Reward, reinforcment
Opioids	Pleasure, urges

Biochemistry

Multiple factors, including behavioral initiation, arousal, reward and reinforcement, and behavioral disinhibition, have been described as contributing to or disordered gambling behavior in PG (38). Unique roles for specific neurotransmitters have been hypothesized as mediating aspects of PG and other ICDs (Table 120.1). Specifically, serotonin (5-HT) has been described as important in behavioral regulation (behavioral initiation and inhibition, including control of aggressive and other impulses) (38–41). Data support a central role for norepinephrine (NE) in the control of levels of arousal and detection of novel or aversive stimuli (42). Multiple lines of evidence from studies of human and other organisms cite dopamine (DA) function, particularly within the mesocorticolimbic (MCL) pathways, as critical in processing and modulating rewarding and reinforcing stimuli and behaviors (43–45). Abnormalities in these neurotransmitter systems as they relate to PG are explored in the following sections.

Serotonin

A role for 5-HT system dysfunction in the neurobiology of PG has come from results of pharmacologic challenge studies (38,46). The 5-HT and NE reuptake inhibitor clomipramine (CMI) has been used to investigate neurochemical responses in individuals with PG as compared with those without PG (46). Eight men and women with PG and eight age- and gender-matched controls received a relatively low intravenous dose of clomipramine (12.5 mg), one that the authors argued targeted primarily the 5-HT transporter (46). The persons with PG in comparison with controls were found to have at baseline lower prolactin levels and exhibited significantly blunted prolactin increases 60 minutes after clomipramine administration (46). The blunted prolactin response suggests the possibility of diminished 5-HT transporter binding in individuals with PG.

An independent challenge study investigating 5-HT function in individuals with PG was undertaken by DeCaria and colleagues (38). The investigators administered metachlorophenylpiperazine (m-CPP) to 10 men with PG and 10 healthy male control subjects. m-CPP, a metabolite of the antidepressant trazodone and a partial 5-HT_1 and 5-HT_2 receptor agonist, binds with high affinity to 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors, with particularly high affinity for 5-HT_{2C} receptors (47–49). 5-HT_{2C} receptors, localized to brain regions including the cortex and caudate, have been implicated in mediating aspects of mood, anxiety, appetite, behavior (including sexual activity), and neuroendocrine function (50,51). The investigators found that individuals with PG reported a euphoric response or ''high'' after m-CPP administration, a finding similar to those reported for other disorders such as antisocial personality disorder (52), borderline personality disorder (53), trichotrillomania (54), and alcohol abuse or dependence (55), in which impulsive or compulsive behaviors are prominent. In addition to differences in behavioral reactions, PG subjects demonstrated altered biochemical responses to the m-CPP challenges. Specifically, increases in prolactin levels were observed in persons with PG, with greater prolactin responses correlating with increased gambling severity.

Additional support for 5-HT dysfunction in individuals with PG has been obtained from investigations of cerebrospinal fluid (CSF) (56). Initial studies into the chemical composition of CSF from men with PG found no significant differences in levels of 5-HT or its metabolite 5-hydroxyindolacetic acid (5-HIAA) as compared to levels in healthy men (57–59). Given that multiple factors can complicate evaluation of CSF data (56,60,61) and the finding that men with PG have significantly longer CSF tapping times than healthy male controls (62), the authors calculated the concentrations of monoamine metabolites per minute of tapping to obtain an estimate of mass flow through the lumbar puncture needle. When taking tapping time into account, levels of 5-HIAA, as well as those of the NE metabolite 4-hydroxy-3-methoxyphenyl glycol (HMPG), were found to be significantly lower in the group of men with PG. These findings, particularly in light of reports of low CSF levels of 5-HIAA in individuals with impulsive characteristics, such as those attempting suicide (39–41), lend further support to a central role for 5-HT in the underlying pathology of PG. Additional data emerging from pharmacotherapy trials, neuroimaging studies, and investigations into monoamine oxidase (MAO) function (see later) are also consistent with 5-HT dysfunction in PG. Further studies are needed to define the nature and extent of 5-HT perturbations in PG more precisely, particularly as they relate to specific aspects of PG (e.g., behavioral initiation or cessation) and subgroups of individuals with PG (e.g., as distinguished by such characteristics as gender or comorbid diagnosis).

Dopamine

Data support positing a role for DA in reinforcing and rewarding aspects of gambling in PG. Multiple lines of evidence from studies investigating the neurochemical bases of drug use disorders have implicated the MCL DA system in the mediation of rewarding and reinforcing behaviors (43–45). Studies in humans with cocaine dependence have found MCL regional brain activations after a cocaine-induced rush (63) or viewing of cocaine-related videotapes (64), and occupancy of the DA transporter has been correlated with cocaine's euphorigenic effects (65). A role for DA in the rewarding and reinforcing aspects of gambling has been proposed (38,66). To explore this hypothesis, Bergh et al. analyzed CSF from ten men with PG and seven matched male controls (59). Decreased levels of DA and increased levels of the DA metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were observed in the PG subjects (59). The authors concluded these findings to be consistent with an increased rate of DA neurotransmission, although more recently the same group did not find decreased HVA levels when correcting for CSF flow rate (56).

A separate study investigated peripheral levels of DA under gaming conditions (67). Plasma levels of DA were measured when subjects played Pachinko machines, described as a popular form of recreation in Japan and one that combines elements of pinball and slot machines. The authors reported that after a winning streak described as a ''fever,'' six men who were regular Pachinko players were found to have elevated levels of DA. The authors suggested the DA changes may be related to the motivational processes underlying repeated Pachinko playing. Alterations in measures of arousal, NE, endogenous opiates, and immune system function were also described. Although the results of the foregoing studies and additional evidence from neuroimaging and molecular genetic studies suggest DA dysfunction in PG (see later), more studies are needed to clarify the involvement of DA pathology in PG.

Norepinephrine

NE has been hypothesized as mediating aspects of arousal, attention, and sensation seeking in individuals with PG (38, 57,58,68). To investigate, Roy et al. measured urinary, peripheral, and central levels of NE or the NE metabolites MHPG and vanillylmandelic acid (VMA) and found the PG subjects to have higher CSF levels of MHPG and higher urinary measures of NE (57). In a subsequent report, the investigators found in the same group of 17 men with PG originally studied, scores of extraversion on the Eysenck Personality Questionnaire were found to correlate positively and significantly with CSF and plasma levels of MHPG, urinary measures of VMA, and the sum of urinary levels of NE and NE metabolites (58). More recently, increased CSF

levels of NE and MHPG were found in a second group of men with PG (59), although a subsequent report from the same research team reported findings of decreased MHPG in men with PG when correcting for CSF flow.

As mentioned in the section on DA, a study of male Pachinko players found NE system changes under gaming conditions (67). Specifically, blood levels of NE were found to increase from baseline over time during Pachinko play, with statistically significant changes noted at the onset and end of Pachinko "fever." Levels of NE decreased but remained significantly elevated 30 minutes after the end of "fever." Alterations in heart rate, a physiologic measurement associated with arousal, was also observed, with peak heart rate measured at the start of "fever."

Monoamine Oxidase Activity

The MAOs, subtypes MAO A and MAO B, are enzymes that metabolize NE, 5-HT, and DA (69). Peripheral MAO derived from platelets is of the MAO B subtype and has been suggested to be an indicator of 5-HT function (70, 71), although MAO B also binds with high affinity to and catabolizes DA (69). Decreased platelet MAO activity has been reported in association with impulsive behaviors (72, 73), high levels of sensation-seeking (74–76), and ICDs, including eating disorders (77). Individuals with PG have also been reported to exhibit decreased platelet MAO activities (78,79). In one study, 15 men with PG were found to have MAO activities 26% lower than those in a group of 25 male controls (78). A separate study involving 27 men with PG found MAO activity levels 41% lower than in matched male controls (79). Each group investigated personality and sensation-seeking characteristics of the PG and control groups and found statistically significant differences. However, no clear picture emerged regarding correlation of the characteristics with MAO levels, with no associations maintained after Bonferroni correction application in one study (79) and a positive correlation between MAO and several measures of sensation-seeking in the other (78).

Stress Response Pathways

Immune system and cortisol changes have been related to gaming behaviors. The foregoing study involving Pachinko players (67) found alterations in T cells (decreased number of T cells and decreased CD3-56 activity) and natural killer cells (increased number of natural killer cells without change in activity). A separate study of male and female Kimberley aborigines found significantly higher cortisol levels on days in which gambling behavior was concentrated (Thursdays and Fridays) as compared with temporally distinct days (Mondays and Tuesdays) (80). Significantly higher epinephrine levels were also found on the gambling-concentrated days, a finding further implicating adrenergic function in gambling behaviors. Although higher on gambling-concentrated days, differences in blood pressure measurements did not reach statistical significance. A separate study found no evidence of abnormal cortisol responsivity on a dexamethasone suppression test in 21 men with PG (81). Independently, CSF levels of corticotropin-releasing hormone and corticotropin were found not to be significantly different between healthy and PG-affected men (57). Additional studies investigating immune and stress hormone function in gambling and PG situations are warranted, in light of the foregoing data and reports of increased rates of physical health problems in individuals with PG (82).

Opioidergic Pathways

Given (a) the role of endogenous opioids in mediating levels of pleasure and (b) the μ-opioid receptor (mOR) in modulating reward and reinforcement DA pathways by disinhibition of γ-aminobutyric acid (GABA) input to DA neurons in the ventral tegmental area (83,84), studies exploring β-endorphin function in gaming behaviors has been explored. In the previously detailed Pachinko study (67), blood levels of β-endorphins were found to be elevated during Pachinko play, peaking during the start of "fever." These findings, in conjunction with the results from preliminary studies of the mOR antagonist naltrexone in the treatment of PG (see later), suggest further investigation into opioid function in PG are warranted.

Other Neurotransmitter Systems

Studies of the possible dysregulation of other neurotransmitter systems as related to PG have been undertaken. results of most of these studies to date have been negative, with statistically nonsignificant differences observed between PG and healthy male subjects with regard to CSF levels of neuropeptide Y (57,85), galanin (86), GABA (87), "diazepam-inhibitor binding" (57,88), neurotensin (57) , somatostatin (57), or growth hormone–releasing hormone (57). One study did find decreased levels of the inhibitory neurotransmitter taurine in the CSF of men with PG as compared with healthy controls (89).

Neuroimaging Studies

Few neuroimaging studies directly investigating PG have been performed to date. One study investigated the potential role of the MCL DA system in a study in which participants were paid increasing amounts of money depending on the skill level reached while playing a video game (90, 98). Positron emission tomography (PET) studies using ^{11}C-labeled raclopride, a ligand with high affinity for D2-like DA receptors (D2Rs), found decreased levels of striatal binding in eight male study subjects playing a tank video game as compared with when they viewed a gray screen image (90). The authors concluded that the observed 13%

reduction in [su>11C]raclopride signal during the gaming condition is consistent with at least a twofold increase in levels of extracellular DA. Because the game involved increasing monetary reward associated with each skill level reached during the video game, the paradigm is similar but not identical to actual gambling.

An independent study investigated for specific DA and 5-HT abnormalities in individuals with PG (91). Using PET, the researchers found decreased striatal binding in PG subjects of [^{11}C]*N*-methylspiperone, a ligand with high affinity for D2Rs and 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors (92). The striatal signal, corresponding to D2R-receptor occupancy, could be explained by multiple, non–mutually exclusive possibilities including decreased numbers of available D2Rs, decreased affinity of D2Rs for the tracer, or increased synaptic concentrations of DA. PG subjects were also found to have impaired performance on multiple neurocognitive tests, including the Halstead-Reitan, Wisconsin Card Sort, Shipley, and California Verbal Learning. Regional cerebral blood flow to the frontal cortex and anterior cingulate was found to be significantly lower in PG as compared with healthy subjects during performance of an auditory continuous performance attention task. These findings are consistent with prior studies implicating involvement of the frontal cortex and anterior cingulate in attention (93), among other processes, and suggest a role for these brain regions in mediating attentional deficits in individuals with PG (35).

Multiple neuroimaging studies into the neural bases of drug use disorders have been performed. Studies of drug craving, a central component in relapsing behavior, have repeatedly identified the involvement of anterior cingulate activation (63,64,94,95), among other brain regions. Studies investigating whether similar brain regions may be involved in PG are under way, with preliminary data suggesting the involvement of parallel neural activities (96,97).

Decision Making

An instrument called the Iowa Gambling Task has been developed and used in investigations into decision making (98–101). The tool involves four piles of cards, each associated with predetermined patterns of rewards and punishments. Selection from two of the piles, each associated with lower rewards and lower punishments, will ultimately result in long-term gains, and selection from the other two piles will result in long-term losses. Without prior instruction into the reward and punishment profile of each pile, individuals are instructed to select from the piles and to maximize gains. Interestingly, individuals with stroke lesions in either the ventromedial prefrontal cortex (VM) or amygdala perform worse than healthy subjects on the task (100,101). Additionally, those with VM lesions not only do not improve over time with repeat performance, but also fail to exhibit changes in skin conductance associated with the decision-making processes (102). Individuals with substance use disorders also have demonstrated impaired performance on the Iowa Gambling Task (103–105), and poor performance has been shown to correlate with decreased blood flow measurements to the VM in cocaine-dependent subjects (105,106). The extent to which dysfunction of the VM, amygdala, or other brain regions involved in regulation of emotion and decision making may be involved in the pathophysiology of PG remains to be explored more completely.

Genetics

Twin studies investigating disordered gambling behaviors have been published (107,108). One study observed significantly greater rates of similarities in male monozygotic as compared with male dizygotic twins with regard to participation in past-year high-action forms of gambling (e.g., casino card, lottery, or gambling machine) (108). No differences were observed in the two groups of males with regard to measures of low action forms of gambling or in female monozygotic versus dizygotic groups with regard to past-year participation in either high- or low-action forms gambling. A larger study used the monozygotic (n = 1,869 pairs) and dizygotic (n = 1490 pairs) twins who served in the military in the Vietnam War era on whom questions pertaining to PG from the Diagnostic Interview Schedule Version III-R were available (107). The authors found inherited factors to contribute between 35% and 54% of the liability for each of the five individual PG-related factors. Higher degrees of familial contribution were estimated for the reporting of three (56%) or four (62%) or more of the individual PG-related factors. The results are comparable to findings derived from the same sample for the heritability of drug use disorders, with 34% and 28% of the variance accounted for by genetic and shared environmental factors, respectively (109). The findings reported by Eisen et al. suggest that familial factors explain a substantial portion of the risk for experiencing symptoms or behaviors consistent with PG. The findings are consistent with the notion that genetic influence significantly affects the risk of developing PG.

Molecular genetic investigations into the origin of PG have been performed (110–115). Investigations described to date have been association studies exploring the involvement of genes related to NE, 5-HT, and DA systems. The first of these studies investigated a role for the *D2A1* allele of the D2R, an allele previously reported by the same research group to be implicated in such compulsive-addictive behaviors as drug abuse, cocaine abuse, and compulsive eating and smoking (116,117). In a group of 171 whites with PG, 50.9% carried the *D2A1* allele as compared with 25.9% of the control group (odds ratio (OR) = 2.96; p .0000001) (110). Additionally, gambling severity was found to correlate with an increased likelihood of carrying the *D2A1* allele,

and the group of individuals without compared with those with a history of a major depressive episode were more likely to carry the *D2A1* allele (110). This latter finding suggests that differences in underlying motivations for gambling and comorbidity may be important factors in relation to the genetics of PG.

Comings and colleagues also investigated associations of PG with polymorphic variants of the D1, D3, and D4 receptors (111,112,115). The authors found the frequency of the *Dde I* allele of the D1 receptor (D1R) to be significantly higher as compared with controls in each of three groups: pathologic gamblers, tobacco smokers, and Tourette syndrome probands (111). A negative association for heterozygosity at the *Dde I* polymorphism was observed for all three disease groups. Given the findings of this (111) and their prior study (110) and the roles of the D1R and D2R in modulating rewarding and reinforcing behaviors (118), the authors proposed for the genetic variants at the D2R and D1R with regard to PG the possible existence of heterosis. *Heterosis,* with regard to populations, refers to a situation in which the progeny (hybrid) has a significantly greater effect on phenotype than either parental strain (e.g., certain hybrid strains of corn exhibiting increased vigor) (115). More investigations are needed to replicate the findings in other populations of individuals with PG and to determine the functional significance of the findings.

Allelic variants of the D4 receptor (D4R) differing in the number of 48-base pair nucleotide repeats have been implicated in some studies of novelty-seeking behavior (119,120), but not others (121–124). Moreover, the corresponding proteins derived from the allelic variants demonstrate functional differences (125), a finding lending further support to the concept that differences in the genetic composition of the groups at the D4R site may be directly related to differences in D4R function. Two groups have independently investigated a role for the D4R in PG (113,115), with each group finding differences in groups of individuals with PG. Perez de Castro and colleagues reported a significant positive association between PG and the longest allele of the D4R (D7), with a stronger association observed in the female group and a nonsignificant relationship seen in the male group (113). Conversely, Comings and colleagues reported no significant association between the D7 allele carriers and PG, although a significant positive association was found with regard to the number of individuals with a high number of 48-base pair repeats (five to eight) and PG (115). The authors also reported an increase in heterozygosity at the D4R allele in association with PG, invoking the notion of heterosis. Discrepancies in the findings of the two groups may be explained by genetic heterogeneity, or the genetic contributions from these loci may be additive or modest. Taken together, the findings support a potential role for the D4R in PG, and further studies are warranted to clarify the relationship. Comings and colleagues also found a decrease in heterozygosity of the *Msc I* allele of the D3 receptor individually in groups with PG or Tourette syndrome (112). The multiple genetic findings implicating dopaminergic genes in PG lend further support for a role for DA in PG.

Molecular studies have been performed with regard to genes involved in modulating 5-HT function (112,114). One report did not find a statistically significant association between PG and allelic variants of the tryptophan 2,3-dioxygenase gene, whose gene product regulates 5-HT metabolism (112). A variant of the 5-HT transporter (5-HTT) promoter region (126), associated with altered protein expression (127), was previously implicated in anxiety (127) and depression (128). Specifically, individuals with at least one copy of the short variant, associated with decreased protein levels, were found to have higher measures of anxiety or depression (127,128). Ibanez and Perez de Castro and their colleagues reported an increased association between the short (less functional) variant and PG in the group of males but not females studied, with increasing association observed with increasing severity of PG (129). These findings (a) further support a role for 5-HT dysregulation in PG and (b) suggest the direct target of 5-HT reuptake inhibitors (SRIs), drugs with apparent efficacy in the treatment of PG (see later), may be differentially regulated in certain groups with PG. Further studies are warranted to replicate and extend these findings.

Treatment

Multiple interventions, including imaginal desensitization (130) and aversion therapies (131), have been examined for the treatment of PG (132). Many treatments explored to date have often been inadequate. Arguably the most long-standing form of treatment, Gambler's Anonymous (GA), is associated with an 8% 1-year retention rate, with most participants leaving after one or two meetings (133). Preliminary results of investigations into the efficacy of cognitive behavioral therapy appear promising (134,135), although additional studies, particularly with regard to and in conjunction with pharmacotherapies, are warranted.

Psychopharmacology

Relatively few investigations have been performed into the tolerability and efficacy of drug treatments for PG (Table 120.2). Although most studies involve case reports or series, larger-scale, placebo-controlled trials are emerging.

Mood Stabilizers

Lithium, a salt with mood stabilizing properties believed to modulate 5-HT systems (136), has been examined in the treatment of PG (137). In three men with PG and comorbid cycling mood disorders, lithium, at daily doses reported up to 1,800 mg per day, was found to be at least partially effective in controlling gambling, cycling mood, hypomania

TABLE 120.2. PSYCHOPHARMACOLOGIC TRIALS IN PATHOLOGIC GAMBLING

Catagery	Reference	Drug	Sample	Design	Outcome
Mood stabilizers					
	Moskowitz, 1980 (137)	Lithium	3 males with comorbid cycling mood disorders	Open-label	Improved control of gambling, cycling mood, risk taking, and mania/hypomania
	Haller & Hinterhuber, 1994 (138)	Carbemazepine	1 male	Placebo-controlled, double-blind, crossover	Decreased gambling behavior maintained at 30 wk
Serotonin reuptake inhibitors					
	Hollander, et al., 1992 (140)	Clomipramine	1 female with comorbid social phobia	Placebo-controlled, double-blind, crossover	Gambling behaviors discontinued persisting through 38 wk
	Hollander, et al., 1998 (141)	Fluvoxamine	16 subjects entered, 10 completed (4 female, 6 male)	Placebo-controlled, single-blind, 16-wk trial (8-wk placebo, 8-wk active)	Seven of 10 completers determined to be responders by PG-CGI and PG-YBOCS scores
	Hollander, et al., 2000 (142)	Fluvoxamine	15 subjects enrolled, 10 completed (10 male)	Placebo-controlled, double-blind, crossover (1-wk placebo Lead-in, 8-wk active/ placebo, 8-wk crossover)	Seven of 10 completers determined to be responders by PG-CGI and PG-YBOCS scores; fluvoxamine superior to placebo, particularly at end of 16 wk of treatment
	Blanco-Jerez, et al., 1999 (143)	Fluvoxamine	34 subjects enrolled	Placebo-controlled trial of 6 mo	No statistically significant difference in response rates for placebo as compared with active drug; high rates of discontinuation were seen
	De La Gandera, et al., 1999 (144)	Fluoxetine	20 subjects enrolled (11 receiving drug and psychotherapy, 9 psychotherapy only)	Open-label trial of 6 mo	Fluoxetine plus psychotherapy better than psychotherapy alone at 6 mo as measured by CGI scores and other measures
	Kim, 2000 (145)	Paroxetine	41 subjects (20 receiving paroxetine, 21 placebo)	Placebo-controlled, double-blind, parallel group (1-wk placebo lead-in, 8 wk of active medication of placebo)	Paroxetine group significantly improved as compared with placebo as determined by CGI; no statistically significant difference on other outcome measures
Opioid antagonists	Kim, 1998 (152)	Naltrexone	1 male with comorbid compulsive shopping behavior	Open-label	Gambling and excessive shopping behaviors eliminated at 100 mg/d with gains maintained through 9 mo
	Crockford & El-Guebaly, 1998 (153)	Naltrexone	1 male with comorbid alcohol dependence and depression	Open-label	Cessation in gambling and alcohol cravings observed through 4 wk following addition of naltrexone to fluoxetine

CGI, clinical global impression; PG, pathologic gambling; YBOCS, Yale-Brown Obsessive-Compulsive Scale.

and mania, and risk-taking behaviors. Durations of treatment were not clearly specified, although at least one patient was maintained for up to 1½ years. No adverse effects were described. The author concluded that lithium may target "an affective component with excitability and impulsiveness-explosiveness." Larger controlled studies seem warranted and are currently ongoing to determine the tolerability and efficacy of lithium, particularly in groups of individuals with PG and cycling mood disorders.

A case report involving the use of carbamazepine in the treatment of a 37-year-old man with PG has been described (138). The gambler had a 16-year history of significant gambling, with periods of abstinence lasting only 2 to 3 months apiece despite participation in GA, behavior therapy, and psychoanalysis. A placebo-controlled, double-blind trial of carbamazepine was undertaken, with no improvement noted in gambling behavior over the 12-week placebo phase. Carbamazepine was introduced at 200 mg per day was increased to 600 mg per day, with blood levels of 4.8 to 9.5 μg/mL achieved. Gambling behaviors decreased 2 weeks into treatment, and gains were maintained at 30 months.

Serotonin Reuptake Inhibitors

Given the efficacy of SRIs in targeting OC behaviors in OCD (139) and the data supporting 5-HT dysregulation in PG, trials of SRIs have been performed. The first of these studies involved a 31-year-old woman with PG and comorbid social phobia and OC personality traits who had been gambling persistently despite multiple prior treatments (140). Clomipramine was administered in double-blind, placebo-controlled fashion in a crossover design. Minimal improvement was seen after 10 weeks of placebo treatment. After initiation of active drug at 25 mg per day with an increase up to 175 mg per day, gambling behavior was discontinued at week 3, with absence of gambling remaining at 38 weeks. The adverse effect of increased irritability was effectively treated with a temporary decrease in dose.

More recently, a single-blind crossover study of the selective SRI (SSRI) fluvoxamine was performed (141). Sixteen subjects entered the 16-week trial (8-week placebo lead-in, 8-week active), with seven of ten completers judged to be responders by (a) a score of "much improved" or "very much improved" on the Clinical Global Impression score for gambling severity (PG-CGI) and (b) greater than 25% reduction in scores on the PG modification of the Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS). Of the completers, four were female and six were male. The medication was well-tolerated, and the average dose for completers was 220 mg per day at endpoint, with responders tending to be treated with a slightly lower dose (207 mg per day on average). Noncompleters left the study during the placebo phase (four for noncompliance, two for lack of response). Of the three nonresponders, two were the only completers with histories of cyclothymia, a finding raising the possibility that individuals with a comorbid cycling mood disorder may respond better to an alternate pharmacotherapy. Further studies are warranted to investigate this possibility.

Hollander and colleagues performed a randomized double-blind, placebo-controlled crossover study of fluvoxamine in the treatment of PG (142). The trial lasted 16 weeks after a 1-week placebo lead-in phase, with subjects randomized to receive either active medication or placebo during the first 8-week phase followed by the alternate treatment during the second 8-week phase. Fifteen subjects meeting the criteria for PG but not for active substance use disorders or past or present major axis I disorders were enrolled, and 10 individuals (all male) completed the study. Two of the five noncompleters left during the placebo lead-in phase, one during placebo treatment in phase I, and two during phase I treatment with fluvoxamine (one for noncompliance, one for interaction with an as-needed medication). Study drug dosing was initiated at 50 mg per day, with fixed increases to 100 and 150 mg per day during the second and third weeks, respectively. Thereafter, the dose was adjusted in 50-mg increments each week with a maximum of 250 mg per day and a minimum of 100 mg per day, based on clinical response and drug tolerance. Mean endpoint dose of fluvoxamine was 195 ± 50 mg per day (range, 100 to 250 mg per day). Adverse effects documented during fluvoxamine treatment were of only mild intensity and were consistent with SSRI treatment, and they were not associated with early withdrawal from the study. Outcome measures included scores from the PG-CGI and PG-YBOCS, as earlier. Data from the investigation demonstrated active drug to be superior to placebo in targeting gambling behavior over time. Both the groups receiving active medication and placebo showed improvement in control of gambling behaviors during the first 8 weeks, and the most significant difference in response was observed at the end of the second 8-week block (Fig. 120.2). In other words, during phase II, improvements seen during the course of the 16-week trial in the placebo-fluvoxamine treatment group were more likely to persist over time, whereas initial gains observed in the fluvoxamine-placebo treatment group declined. These findings are consistent with a high initial rate of placebo responders and suggest that acute trials of longer duration may be important in better distinguishing response to placebo and active drug.

A longer-term placebo-controlled trial of fluvoxamine in the treatment of PG was reported by an independent group (143). In their study, 34 patients were treated for 6 months with placebo or fluvoxamine at 200 mg per day. Outcome was measured by quantification of time and money spent on gambling. The authors found no statistically significant differences in response rates to placebo as compared with active drug for the overall sample. The authors reported observing a statistically significant superiority of fluvoxamine as compared with placebo in the male and younger-aged subgroups of individuals with PG in the study. Strik-

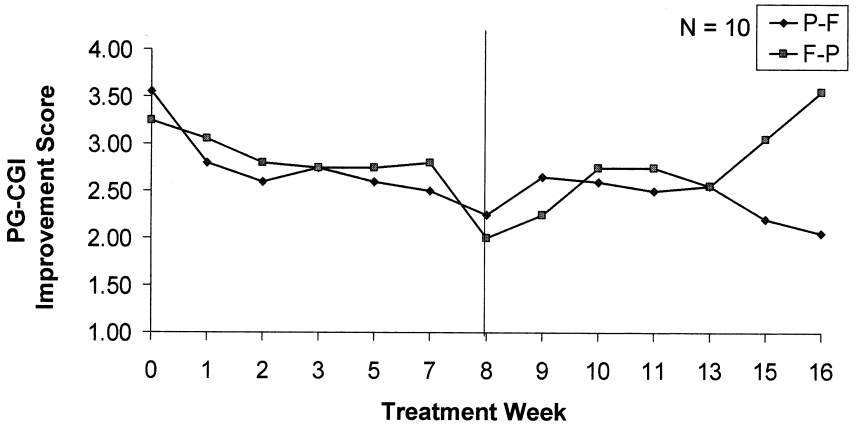

FIGURE 120.2. Changes in gambling symptom severity of patients with pathologic gambling (PG) in response to fluvoxamine. Changes in PG–Clinical Global Impression (CGI) scores are shown for subjects completing a 16-week placebo-controlled, double-blind study of fluvoxamine for the treatment of PG. Measures are shown for individuals receiving placebo in phase I followed by fluvoxamine in phase II *(diamonds)* or fluvoxamine in phase I followed by placebo in phase II *(squares).* ANOVAR: [$F = 14.8$ (df = 1,8), $p = .005$ (drug effect)]; ANOVAR: [$F = 6.0$ (df = 1,8), $p = .040$ (phase order × drug interaction)]; *post hoc* ANOVA: phase I: [$F = 0.113$ (df = 1,7), $p = .747$]; phase II: [$F = 12.45$ (df = 1,7), $p = .010$].

ingly, a large proportion of individuals did not complete the 6-month study, and this complicated interpretation of the results and suggested that long-term compliance with drug treatment will be a significant consideration for individuals with PG.

A separate longer-term, open-label trial of a different SSRI, fluoxetine, was performed (144). The study compared the results of treatment with fluoxetine at 20 mg per day with support psychotherapy (n = 11) as compared with psychotherapy alone (n = 9). Measures of outcome included scores on the CGI and Ludo-Cage test. The treatment group receiving fluoxetine showed significantly improved outcomes as measured by CGI scores (fluoxetine plus psychotherapy: 1.5 ± 0.8; psychotherapy alone: $3.2 \pm > 0.7$; $p < .001$) and Ludo-Cage mean scores ($p = .004$) at the 6-month assessments. Individuals in the combined fluoxetine and psychotherapy treatment group also demonstrated better adherence to treatment guidelines.

An independent double-blind, placebo-controlled trial of a third SSRI, paroxetine, was performed (145). The study used a parallel group design with each group receiving a 1-week placebo lead-in followed by 8 weeks of either placebo or active medication. Dosing was initiated at 20 mg per day with increases up to 60 mg per day as clinically indicated. Forty-one patients meeting the criteria for PG and no other axis I diagnosis participated in the study (20 paroxetine, 21 placebo). Adverse effects were observed with greater frequency in the paroxetine-treated group (2.3 treatment-emergent symptoms per patient in the paroxetine group as compared with 1.2 in the placebo group). The treatment-emergent symptoms were consistent with SSRI treatment, most frequently involving reports of headaches, fatigue, and dry mouth. Outcome was measured by scores on the patient- and clinician-rated CGI and the Gambling Symptom Assessment Scale (G-SAS). The paroxetine treatment as compared with placebo resulted in statistically significant improvement as determined by the clinician-rated CGI (random regression analysis: $z = -1.99$, $p < .05$), with no statistically significant differences observed between groups on other measures.

Taken together, findings from these initial studies suggest that SSRIs are well-tolerated, efficacious drugs for the treatment of PG. Larger scale (e.g., multicenter), placebo-controlled trials of SRIs are warranted to extend these initial promising results and to define better the short- and long-term efficacies and tolerabilities of specific SRIs in groups of individuals with PG.

Opioid-Receptor Antagonists

The mOR, involved in regulation of DA reward- and reinforcement-related pathways, has been the target for pharmacotherapies in the treatment of addictive disorders. Naltrexone, an mOR antagonist, has been shown to reduce alcohol intake and alcohol cravings in the treatment of alcohol dependence (146–148), as well as to target impulsive, self-injurious behaviors in multiple other patient populations (149–151). Two case reports described a potential role for naltrexone in the treatment of individuals with PG (152, 153). In an open-label case series of individuals with ICDs, Kim described a 55-year-old man with PG and CB (152). Naltrexone at 50 mg per day was initiated with no clinical change observed at 2 weeks. Several days after an increase to 100 mg per day, a significant decrease in gambling urge intensity was reported by the patient. This decrease was followed by elimination of gambling and excessive buying, with gains maintained for at least 9 months.

An independent case report described the open-label treatment of a 49-year-old man with comorbid PG, depression, and alcohol dependence (153). The patient was initially treated with fluoxetine (dose and duration not specified), with improvements in mood and persistence in urges to drink and gamble. Naltrexone at 50 mg per day was added to the fluoxetine with a cessation in gambling and alcohol cravings observed over a 4-week period. Given the data supporting gambling-induced opioidergic changes (67), the role of opioid function in modulating DA reward

and reinforcement pathways, and the results of the present study, larger-scale, placebo-controlled trials of mOR antagonists seem warranted.

COMPULSIVE BUYING

Although recognized by Kraeplin and Bleuler a century ago, CB, then termed oniomania and more recently compulsive shopping or impulsive or addictive buying, has been relatively understudied in psychiatry (154–156). Although not formally listed in the DSM-IV (1), CB has a set of proposed diagnostic criteria (157), which include maladaptive preoccupation with or engagement in buying and the preoccupations or actual buying leading to significant distress or impairment. Additionally, the behavior cannot be better accounted for by a manic episode. Prevalence estimates have been made at 1% to 8% of the general population (157–159). Initial reports describe individuals with CB as generally in their thirties and predominantly female, with a 4:1 or greater female-to-male ratio (156,159,160). Individuals with CB are reported to have elevated rates of psychiatric comorbidity, particularly anxiety disorders, mood disorders, substance abuse or dependence, eating disorders, ICDs, and personality disorders (157,159,161).

Pharmacotherapy

Thymoleptic Treatment

Some authors have proposed depression as a significant underlying motivational factor related to engagement in CB (158,162,163). An early description of pharmacotherapeutic interventions in PG described the use of three antidepressant medications, fluoxetine, bupropion, and nortriptyline, in CB (164). Each of the three patients receiving the medications reported a partial or complete reduction in CB symptoms. In a larger study of 20 individuals with CB, nine of 13 patients who had received thymoleptic pharmacotherapy while they were symptomatic (69%) reported their CB to be in full (n = 5) or partial (n = 4) remission (157). The 20 study participants were predominantly female (n = 16) and often carried active comorbid diagnoses, most frequently mood (n = 18) or anxiety (n = 12) disorders. The effective drugs used varied widely and included bupropion, lithium, valproate, nortriptyline, desipramine, fluoxetine, sertraline, trazodone, clonazepam, diazepam, levothyroxine, and methylphenidate, often used in combination of two or more drugs simultaneously (157). Doses and durations of pharmacotherapy were not clearly defined in the report. The authors described full remissions up to only 7 months and partial remissions up to 13 months and noted that several of the drug trials were terminated after only a short period secondary to intolerable adverse effects (n = 2) or hypomania (n = 1). Although the relationship between pharmacotherapy and CB symptoms cannot be precisely determined from the study, the findings support the need for further systematic investigations into drug treatments for CB.

Selective Serotonin Reuptake Inhibitors

Given the repetitive, ritualistic buying behaviors and the intrusive preoccupations with buying associated with CB, the efficacy of SSRIs in the treatment of OCD, and the initial findings with SSRIs described earlier, an open-label trial of fluvoxamine in CB was undertaken (165). The ten participants in the study met the criteria for CB, as proposed by McElroy et al. (157), and not for an active mood or substance use disorder. Nine participants were female, and the average age of the group was 41.4 ± 9.2 years. The study design included a 1-week placebo lead-in followed by an 8-week period of treatment with fluvoxamine and a subsequent drug taper and discontinuation (over 3 to 4 days) and reassessment off medication at the end of week 13. Responses were measured with the YBOCS modified for CB (YBOCS-SV), the CGI, patient self-rating, and other standardized scales for depression, disability, and OC symptoms. Nine of ten individuals were deemed responders, having a more than 50% reduction in YBOCS-SV scores at week 9 as compared with baseline. Highly significant improvements were observed at week 9 as compared with baseline in scores on both the obsession and compulsion subscales of the YBOCS-SV, the National Institute of Mental Health OC scale, patient self-rating reports, subscales of the Sheehan Disability Scale, and the CGI severity and improvement scales. Symptoms appeared to worsen but often remained improved from baseline during the 4-week discontinuation phase. The adverse effects reported were consistent with fluvoxamine's use in other patient populations, with sedation, headache, dry mouth, and gastrointestinal disturbances reported most frequently. The appearance of adverse effects did not result in discontinuation of the drug for any of the participants. The results from this initial study of fluvoxamine in the treatment of CB suggest it to be efficacious and well-tolerated and support the need for larger scale, placebo-controlled, double-blind studies of SSRIs in CB.

Opioid Antagonists

Given data supporting efficacy of the μ-opioid antagonist naltrexone in urge regulation and the role of μ-opioid function in modulating MCL DA pathways, a trial of naltrexone in the treatment of ICDs (including CB) was reported (152). Two patients with CB treated with naltrexone were described in detail in a series of 15 individuals with ICDs, with an additional three responders with CB mentioned in the report. One of the two responders had comorbid PG and CB, and this response is described earlier (in the PG

section). A second individual, a 46-year-old woman with comorbid CB and bulimia nervosa, was started on naltrexone at 50 mg per day. She initially developed diarrhea, which later resolved without discontinuation of the drug. After not experiencing improvement in target symptoms, her dose was increased to 100 mg per day at week 2. At this dose, she reported a significant decrease in thoughts and behaviors related to excessive shopping and disordered eating. She maintained her gains at 7 months and tolerated the medication with normal liver function tests and without adverse effects. The results from this initial report of open-label, high-dose naltrexone administration suggest that the drug may be effective in targeting symptoms of CB. Larger-scale, placebo-controlled, double-blind studies are warranted to define better the efficacy and tolerability of the drug in the short- and long-term treatment of individuals with CB.

COMPULSIVE SEXUAL BEHAVIOR

Traditionally, the majority of attention given to disordered sexual behaviors has arguably been focused on the paraphilias. These disorders involve sexual arousal from inappropriate objects or partners and include fetishism, exhibitionism, voyeurism, sadomasochism, pedophilia, and zoophilia. Nonparaphilic excessive sexual behavior, currently classified as an ''ICD not otherwise specified'' in the DSM, involves repetitive, interfering sexual behavior without the use of inappropriate objects or partners (166). The term CSB has been used to encompass both paraphilic and nonparaphilic sexual disorders (167). CSB has been estimated to affect 3% to 6% of individuals in the United States (167–169), with most of those with the disorder thought to be male (167,170,171). Given the relatively high estimated prevalence rates and the clinical or social impairment often experienced with CSB, there exists a need for further well-defined studies into the epidemiology and treatment of CSB.

Pharmacotherapy

Thymoleptics

High rates of mood disorders have been reported in individuals with CSB (167,172). Case reports have been described supporting the efficacy of multiple thymoleptics in the treatment of CSB. Specifically, the following have been reported: electroconvulsive therapy (173) and treatments with lithium (174–176), buspirone (177), imipramine (178,179), desipramine (180), clomipramine (180), and the SSRIs (172, 178,181–187), particularly fluoxetine and sertraline. In the following section, we describe one of the larger, systematic investigations performed to date.

Selective Serotonin Reuptake Inhibitors

Initial studies into the efficacy and tolerability of SSRIs in the treatment of paraphilic and nonparaphilic CSBs have been performed (187). In one study, 20 men with CSB were entered into a 12-week open-label trial of fluoxetine (172). Ten of the men had solely nonparaphilic CSBs, and the other ten had both paraphilic and nonparaphilic CSBs. Nineteen met the criteria for comorbid dysthymia and 11 for current major depression. Outcome measures included the Inventory to Diagnose Depression (IDD) and the Sexual Outlet Inventory (SOI). IDD scores were obtained at baseline and weeks 4, 8, and 12. Of the 20 entered participants, four discontinued (three nonparaphilic and one paraphilic, one each for alcohol abuse, no change in CSB, increase in CSB after initial remission, and increased anxiety and CSB). The mean dose of fluoxetine at week 12 was 39.37 ± 14.81 mg per day. Significant reductions in both depressive and CSB symptoms were observed, with improvement in sexual symptoms independent of baseline depression scores. Sexual symptoms showing significant improvement included total sexual outlet and unconventional forms of masturbation, sexual activity, desire intensity, and sexual interests. Conventional sexual symptoms were not adversely effected. The promising results of this open-label study warrant larger, placebo-controlled, double-blind studies of specific subgroups of individuals with CSB to determine further the efficacy and tolerability of fluoxetine and other SSRIs.

Dopamine Augmentation

In individuals who respond incompletely to SSRIs, trials of augmentation with the DA-enhancing drugs methylphenidate or bupropion have been described. The rationale for use of these drugs has been described as related to multiple findings, including the efficacy of similar augmentation strategies in depressive disorders, improvement of SRI-induced adverse effects with these DA ''agonists,'' and comorbidity and similarities with attention-deficit/hyperactivity disorders (172). One investigator reports having treated more than 30 patients with the combination of an SRI and a DA drug (172). Further studies are needed to both explore possible DA dysfunction in CSB and to determine the efficacies and tolerabilities of DA drugs in CSB.

Hormone System Treatments

Several classes of drugs modulating hormonal systems, including antiandrogens, estrogens, and gonadotropin-releasing hormone (GnRH) analogues, have been investigated in the treatment of CSBs (187–193). The group of antiandrogens includes medroxyprogesterone acetate (MPA) and cyproterone acetate (CPA). MPA, a potent progestogen lacking antiandrogen effects at the androgen receptor level, has been tested in targeting CSB (reviewed in refs. 187 and

193). CPA, also a potent progestogen but also with testosterone antagonist activity at the receptor level, has also been studied in the treatment of CSB (190,194). The results of placebo-controlled trials of MPA, CPA, or both (190,194, 195), as well as data from a large number of open-label trials and case reports (reviewed in refs. 187 and 193), suggest a role for the drugs in the management of groups of individuals with CSBs, particularly sex offenders and elderly individuals with aggressive sexual behaviors. Although these agents are not effective for all patients (196), accumulating data suggest this family of drugs may be effective in subgroups of individuals with CSB, particularly those with repetitive deviant sexual behaviors (193). The drugs are limited by the emergence of adverse effects, including commonly weight gain, fatigue, hypertension, headaches, hyperglycemia, leg cramps, and diminished spermatogenesis (187). More rarely, feminizing effects may be seen, and thromboembolic phenomena may be seen more frequently with use of the drugs (187). Additional studies are needed to determine the long-term efficacy and tolerability of the antiandrogen drugs MPA and CPA in nonparaphilic and paraphilic CSBs.

Fewer studies have been performed to date to test the efficacy and tolerability in CSB of estrogens such as diethylstilbestrol (DES) (197) or transdermal estrogen (198) and GnRH analogues such as triptorelin (191) and leuprolide (196). Estrogen treatment works in a similar fashion to MPA and CPA in terms of decreasing luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion and thereby decreasing testosterone production. In contrast, GnRH analogues suppress testosterone production by stimulation of LH and FSH secretion leading to increased testosterone and estrogen levels. Continued administration results in insensitivity of the pituitary to GnRH, significantly reducing LH and FSH levels. One of the larger studies includes an open-label trial of triptorelin in the treatment of 30 men with paraphilic CSB. Treatment of 8 to 42 months' duration with injectable triptorelin at 3.75 mg per month resulted in significant decreases in deviant sexual fantasies and behaviors along with significant decreases in serum testosterone levels (191). Adverse effects included erectile failure, hot flashes, and decrease in bone mineral densities. As with antiandrogens, adverse effect profiles of estrogens and GnRH analogues may preclude widespread use of these classes of drugs in the treatment of CSB. However, a role for these drugs may exist in the treatment of specific subgroups of individuals with CSBs.

COMPULSIVE COMPUTER USE

With the increasing availability of personal computers and the rapid expansion in use of the Internet, the emergence of disordered computer use has been described (199–203). The Internet provides immediate access to a broad range of impulsive behaviors, including gambling (both traditional forms as well as stock trading), shopping, and sexual behaviors, and it may be associated with an increase in the prevalence of related ICDs. Individuals with excessive and interfering computer use have been termed ''webaholics'' or ''cyberholics,'' and their computer-related behaviors have been termed computer or Internet addiction or dependency, Internet addictive disorder, cyberaddiction, or CCU (204–206). Given the recent emergence of CCU, formal diagnostic criteria have not been developed or endorsed, pharmacologic treatment studies have not been reported, and its relationship with other disorders (e.g., OCD, substance use, mood and ICDs) has not been adequately investigated. Nonetheless, initial investigations into the characteristics of individuals with CCU have been performed.

One study using a 94-item questionnaire described four factors relating to CCU in a sample of college students (205). From 341 completed questionnaires, four factors (two major and two minor) were identified and were found to explain 31% of the variance. Factor 1 focused on problematic use of the Internet and included significant contributions from questions relating to staying on line too long, having a restricted repertoire of interests, and interference with sleep, diet, exercise, and attending meetings. Within this factor, lower levels of correlation but each above 0.35 were noted for computer hacking and gambling and use of the Internet to relieve sadness or loneliness. The second major factor focused on the usefulness and general purpose of computers or the Internet. Positive correlations with extensive use of the Internet and finding information loaded onto this factor. Interestingly, questions related to on-line shopping and downloading of nude images loaded onto factor 2, as compared with on-line gambling, which loaded onto factor 1. Given the estimated high rates of Internet use for sexually related activities (1% of a group of on-line computer users spending more than 11 hours per week) (207), definition of the characteristics of ICD-related online behaviors seems particularly important. A positive correlation with campus and negative correlation with home computer use also was observed within factor 2. Factor 3 focused on questions relating to a combination of shyness and introversion and using the Internet for sexual gratification (high correlation with physical arousal and downloading of nude images), whereas factor 4 focused on the absence of Internet problems and a mild aversion to or lack of interest in the technology. These initial findings suggest that some similar motivations that underlie other ICDs may lead to CCU and provide data that could be helpful in defining diagnostic characteristics for CCU.

A second investigation recruited 21 individuals (16 men, five women) with self-reported excessive computer use that interfered with social or occupational functioning or caused personal distress (206). Participants were mainly between 20 and 50 years of age, with 43% of the total sample falling between the ages of 21 and 29 years, inclusively. Observed were high rates of attempting to cut back on computer usage (62%) and comorbid psychiatric illness, including mood,

substance use, anxiety, and personality disorders. The findings of the studies by Black et al. and Praterelli et al. suggest the need for additional studies into the epidemiology and neurobiology of CCU, as well as pharmacologic and behavioral treatments for individuals with CCU.

CONCLUSIONS AND FUTURE DIRECTIONS

Although understudied for a significant period of time by the psychiatric community, PG and other ICDs appear to be receiving an increasing amount of clinical attention. Significantly more research is needed to diminish the gap in our knowledge of ICDs as compared with other psychiatric illnesses and to optimize treatment strategies for the large number of individuals suffering from these disorders.

ACKNOWLEDGMENTS

Dr. Hollander has received research support and/or served as a consultant or on a speaker's bureau for the following companies: Solvay, Abbott, SmithKline Beecham, Lilly, Wyeth-Ayerst and Bristol Myers Squibb.

REFERENCES

1. American Psychiatric Association Committee on Nomenclature and Statistics. *Diagnostic and statistical manual of mental disorders,* fourth ed. Washington, DC: American Psychiatric Association, 1994.
2. Gabriel K. Gambling and spirituality: a new anthropological perspective. *www.nmia.com/~kgabriel/* 1998.
3. Anonymous. *Mahabharata: adiparva.* Ganguli KM, trans. Calcutta and Evanston, IL: Bharata Press and American Theological Library, 1884:647.
4. Weems ML. *God's revenge against gambling exemplified in the miserable lives and untimely deaths of a number of persons from both sexes, who had sacrificed their health, wealth, and honor at the gaming tables.* Philadelphia: 1812.
5. Cosby AG, May DC, Frese W, et al. Legalization of crimes against the moral order: results from the 1995 United States survey of gaming and gambling. *Deviant Behav Interdisc J* 1996; 17:369–389.
6. McElroy SL, Hudson JI, Pope HG Jr, et al. The DSM-III-R impulse control disorders not elsewhere classified: clinical characteristics and relationship to other psychiatric disorders. *Am J Psychiatry* 1992;149:318–327.
7. Hollander E. Treatment of obsessive-compulsive spectrum disorders with SSRIs. *Br J Psychiatry* 1998;173[Suppl 35]:7–12.
8. Hollander E, Wong CM. Obsessive-compulsive spectrum disorders. *J Clin Psychiatry* 1995;56[Suppl 4]:3–6.
9. Hollander E, Wong CM. Body dysmorphic disorder, pathological gambling, and sexual compulsions. *J Clin Psychiatry* 1995; 56[Suppl 4]:7–12; discussion, 13.
10. Hollander E, Benzaquin SD. Is there a distinct OCD spectrum? *CNS Spectrums* 1996;1:17–26.
11. Siever LJ. Relationship between impulsivity and compulsivity: a synthesis. In: Oldham J, Hollander E, Skodol AE, et al., eds. *Impulsivity and compulsivity.* Washington, DC: American Psychiatric Association, 1996:261–272.
12. Linden RD, Pope HG Jr, Jonas JM. Pathological gambling and major affective disorder: preliminary findings. *J Clin Psychiatry* 1986;47:201–203.
13. Simeon D, Hollander E, Cohen L. Obsessive compulsive related disorders. In: Hollander E, Zohar J, Marazziti D, eds. *Current insights in obsessive compulsive disorder.* Chichester, UK: Wiley, 1994:53–66.
14. Rasmussen SA, Eisen JL. *Epidemiology and clinical features of obsessive-compulsive disorder.* Littleton, MA: Medical Publishers, 1990:10–27.
15. Hollander E, Stein DJ, Kwon JH, et al. Psychosocial function and economic costs of obsessive-compulsive disorder. *CNS Spectrums* 1997;2:16–25.
16. Kagan DM. Addictive personality factors. *J Psychol* 1987;121: 533–538.
17. Specker SM, Carlson GA, Edmonson KM, et al. Psychopathology in pathological gamblers seeking treatment. *J Gambling Stud* 1996;12:67–81.
18. Black DW, Goldstein RB, Noyes R, et al. Compulsive behaviors and obsessive-compulsive disorder (OCD): lack of a relationship between OCD, eating disorders, and gambling. *Compr Psychiatry* 1994;35:145–148.
19. Blaszczynski A. Pathological gambling and obsessive-compulsive spectrum disorders. *Psychol Rep* 1999;84:107–113.
20. De Marchi N, Morris M, Mennella R, et al. Association of obsessive-compulsive disorder and pathological gambling with Huntington's disease in an Italian pedigree: possible association with Huntington's disease mutation. *Acta Psychiatr Scand* 1998; 97:62–65.
21. Lesieur HR, Blume SB, Zoppa RM. Alcoholism, drug abuse, and gambling. *Alcohol Clin Exp Res* 1986;10:33–38.
22. Marks I. Behavioural (non-chemical) addictions. *Br J Addict* 1990;85:1389–1394.
23. DeCaria C, Hollander E. Pathological gambling. In: Hollander E, ed. *Obsessive-compulsive related disorders.* Washington, DC: American Psychiatric Association, 1993:155–178.
24. Crockford DN, el-Guebaly N. Psychiatric comorbidity in pathological gambling: a critical review. *Can J Psychiatry* 1998;43: 43–50.
25. McCormick RA, Russo AM, Ramirez LF, et al. Affective disorders among pathological gamblers seeking treatment. *Am J Psychiatry* 1984;141:215–218.
26. Cunningham-Williams RM, Cottler LB, Compton WM 3rd, et al. Taking chances: problem gamblers and mental health disorders—results from the St. Louis Epidemiologic Catchment Area Study. *Am J Public Health* 1998;88:1093–1096.
27. Spunt B, Lesieur H, Hunt D, et al. Gambling among methadone patients. *Int J Addict* 1995;30:929–962.
28. Feigelman W, Kleinman PH, Lesieur HR, et al. Pathological gambling among methadone patients. *Drug Alcohol Depend* 1995;39:75–81.
29. Haberman PW. Drinking and other self-indulgences: complements or counter-attractions? *Int J Addict* 1969;4:157–167.
30. Steinberg MA, Kosten TA, Rounsaville BJ. Cocaine abuse and pathological gambling. *Am J Addict* 1992;1:121–132.
31. Harvard Medical School Division on Addictions. Screening veterans for pathologial gambling. *The WAGER* 1998;3(14):1.
32. Kaplan G, Davis B. *Gambling, alcohol, and other drugs: prevalence and implications of dual problem clients.* Winnipeg, Canada: Addicitions Foundation of Manitoba, 1997.
33. Smart RG, Ferris J. Alcohol, drugs and gambling in the Ontario adult population, 1994. *Can J Psychiatry* 1996;41:36–45.
34. Harvard Medical School Division on Addictions. Screening veterans for pathological gambling. *The WAGER* 1996;1(43):1.
35. Rugle L, Melamed L. Neuropsychological assessment of atten-

tion problems in pathological gamblers. *J Nerv Ment Disease* 1993;181:107–112.
36. Blaszczynski A, McConaghy N, Frankova A. Crime, antisocial personality and pathological gambling. *J Gambling Behav* 1989; 5:137–152.
37. Blaszczynski AP, McConaghy N. Antisocial personality disorder and pathological gambling. *J Gambling Stud* 1994;10:129–145.
38. DeCaria C, Begaz T, Hollander E. Serotonergic and noradrenergic function in pathological gambling. *CNS Spectrums* 1998;3: 38–47.
39. Asberg M, Traskman L, Thoren P. 5–HIAA in the cerebrospinal fluid: a biochemical predictor. *Arch Gen Psychiatry* 1976;33: 1193–1197.
40. Linnoila M, Virkunnen M, Scheinen M, et al. Low cerebrospinal fluid 5–hydroxy indolacetic acid concentrations differentiates impulsive from non impulsive violent behavior. *Life Sci* 1983;33:2609–2614.
41. Coccaro EF, Siever LJ, Klar HM, et al. Serotonergic studies in patients with affective and personality disorders: correlates with suicidal and impulsive aggressive behavior. *Arch Gen Psychiatry* 1989;46:587–599.
42. Usdin E, Snyder S, eds. *Frontiers in catecholamine research.* Elmsford, NY: Pergamon, 1973.
43. Koob GF. Drugs of abuse: anatomy, pharmacology and functions of reward pathways. *Trends Pharmacol Sci* 1992;13: 177–184.
44. Self DW, Nestler EJ. Molecular mechanisms of drug reinforcement. *Annu Rev Neurosci* 1995;18:463–495.
45. Koob GF, Nestler EJ. The neurobiology of drug addiction. *J Neuropsychiatry Clin Neurosci* 1997;9:482–497.
46. Moreno I, Saiz-Ruiz J, Lopez-Ibor JJ. Serotonin and gambling dependence. *Hum Psychopharmacol* 1991;6[Suppl]:9–12.
47. Caccia S, Ballabio M, Saminin R, et al. M-CPP, a central 5–HT agonist, is a metabolite of trazodone. *J Pharm Pharmacol* 1981; 33:477–478.
48. Hamik A, Peroutka SJ. 1–(m-Chlorophenyl) piperazine (mCPP) interactions with neurotransmitter receptors in the human brain. *Biol Psychiatry* 1989;25:569–575.
49. Hoyer D. Functional correlates of serotonin 5–HT1 recognition sites. *J Recept Res* 1988;8:59–81.
50. Kennett GA, Curzon G. Evidence that mCPP may have behavioural effects mediated by the 5HT1C receptor. *Br J Pharmacol* 1988;94:137–147.
51. Kennett GA, Curzon G. Evidence that hypophagia induced by mCPP and TFMPP requires 5HT1C and 5HT1B receptors: hypophagia induced by RU 24969 requires only 5HT1B receptors. *Psychopharmacology (Berl)* 1998;96:93–100.
52. Moss HB, Yao JK, Panzak GL. Serotonergic responsivity and behavioral dimensions in antisocial personality associated with substance abuse. *Biol Psychiatry* 1990;28:325–338.
53. Hollander E, Stein D, DeCaria CM, et al. Serotonergic sensitivity in borderline personailty disorder: preliminary findings. *Am J Psychiatry* 1994;151:277–280.
54. Stein DJ, Hollander E, DeCaria C, et al. Behavioral responses to m-chlorophenyl-poperazine and clonidine in trichotrillomania. *J Serotonin Res* 1997;4:11–15.
55. Benkelfat C, Murphy DL, Hill JL, et al. Ethanol like properties of the serotonergic partial agonist m-chlorophenylpiperazine in chronic alcoholic patients. *Arch Gen Psychiatry* 1991;48:383.
56. Nordin C, Eklundh T. Altered CSF 5–HIAA disposition in pathologic male gamblers. *CNS Spectrums* 1999;4:25–33.
57. Roy A, Adinoff B, Roehrich L, et al. Pathological gambling: a psychobiological study. *Arch Gen Psychiatry* 1988;45:369–373.
58. Roy A, De Jong J, Linnoila M. Extraversion in pathological gamblers: correlates with indexes of noradrenergic function. *Arch Gen Psychiatry* 1989;46:679–681.
59. Bergh C, Eklund T, Sodersten P, et al. Altered dopamine function in pathological gambling. *Psychol Med* 1997;27:473–475.
60. Bertilsson L, Asberg M, Lantto O, et al. Gradients of monoamine metabolites and cortisol in cerebrospinal fluid of psychiatric patients and healthy controls. *Psychiatry Res* 1982;6:77–83.
61. Nordin C, Swedin A, Zachau A. Tapping time influences concentrations of 5–HIAA in the CSF. *J Psychiatr Res* 1993;27: 409–414.
62. Nordin C, Eklundh T. Tapping-time is longer in pathological male gamblers than in healthy male controls. *J Psychiatr Res* 1998;32:421–422.
63. Breiter HC, Gollub RL, Weisskopf RM, et al. Acute effects of cocaine on human brain activity and emotion. *Neuron* 1997; 19:591–611.
64. Maas LC, Lukas SE, Kaufman MJ, et al. Functional magnetic resonance imaging of human brain activation during cue-induced cocaine craving. *Am J Psychiatry* 1998;155:124–126.
65. Volkow ND, Wang GJ, Fischman MW, et al. Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature* 1997;386:827–830.
66. Bergh C, Kuhlhorn E. Social, psychological and physical consequences of pathological gambling in Sweden. *J Gambling Stud* 1994;10:275–285.
67. Shinohara K, Yanagisawa A, Kagota Y, et al. Physiological changes in Pachinko players: beta-endorphin, catecholamines, immune system substances and heart rate. *Appl Hum Sci* 1999; 18:37–42.
68. Zuckerman M. *Sensation seeking: beyond the optimal level of arousal.* Hillsdale, NJ: Lawrence Erlbaum Associates, 1979.
69. Deutch AY, Roth RH. Neurochemical systems in the central nervous system. In: Charney DS, Nestler EJ, Bunney BS, eds. *Neurobiology of mental illness.* New York: Oxford University Press, 1999:10–25.
70. Oreland L, Wiberg A, Asberg M, et al. Platelet MAO activity and monoamine metabolites in cerebrospinal fluid in depressed and suicidal patients and in healthy controls. *Psychiatry Res* 1981;4:21–29.
71. Levitt P, Pintar JE, Braekefield XO. Immunocytochemical demonstration of monoamine oxidase B in brain astrocytes and serotonin neurons. *Proc Natl Acad Sci USA* 1982;79:6385–6389.
72. Buchsbaum MS, Haier RJ, Murphy DL. Suicide attempts, platelet monoamine oxidase and the average evoked response. *Acta Psychiatr Scand* 1977;56:69–79.
73. von Knorring L, Oreland L, von Knorring AL. Personality traits and platelet MAO activity in alcohol and drug abusing teenage boys. *Acta Psychiatr Scand* 1987;75:307–314.
74. Fowler CJ, Von Knorring L, Oreland L. Platelet monoamine activity in sensation seekers. *Psychiatry Res* 1980;3:273–279.
75. Ward PB, Catts SV, Norman TR, et al. Low platelet monoamine oxidase and sensation seeking in males: an established relationship? *Acta Psychiatr Scand* 1987;75:86–90.
76. Carrasco JL, Saiz-Ruiz J, Diaz-Marsa M, et al. Low platelet monoamine oxidase activity in sensation-seeking bullfighters. *CNS Spectrums* 1999;4:21–24.
77. Hallman J, Sakurai E, Oreland L. Blood platelet monoamine oxidase activity, serotonin uptake, and release rates in anorexia and bulimia patients and in healthy controls. *Acta Psychiatr Scand* 1990;81:73–77.
78. Carrasco JL, Saiz-Ruiz J, Hollander E, et al. Low platelet monoamine oxidase activity in pathological gambling. *Acta Psychiatr Scand* 1994;90:427–431.
79. Blanco C, Orensanz-Munoz L, Blanco-Jerez C, et al. Pathological gambling and platelet MAO activity: a psychobiological study. *Am J Psychiatry* 1996;153:119–121.
80. Schmitt LH, Harrison GA, Spargo RM. Variation in epinephrine and cortisol excretion rates associated with behavior in an

Australian aboriginal community. *Am J Phys Anthropol* 1998; 106:249–253.
81. Ramirez LF, McCormick RA, Lowy MT. Plasma cortisol and depression in pathological gamblers. *Br J Psychiatry* 1988;153: 684–686.
82. James KC, Bible WA, Dobson JC, et al. National Gambling Impact Study Commission: final report to Congress. *http://www.ngisc.gov/reports/fullrpt.html* 1999.
83. Phillips AG, LePiane FG. Reinforcing effects of morphine microinjection on to the ventral tegmental area. *Pharmacol Biochem Behav* 1980;12:965–968.
84. von Wolfswinkel L, van Ree JM. Effects of morphine and naloxone on thresholds of ventral tegmental electrical self-stimulation. *Naunyn Schmiedebergs Arch Pharmacol* 1985;330:84–92.
85. Roy A, Berrettini W, DeJong J, et al. CSF neuropeptide Y in alcoholics and normal controls. *Psychiatry Res* 1990;33: 215–219.
86. Roy A, Berrettini W, Adinoff B, et al. CSF galanin in alcoholics, pathological gamblers, and normal controls: a negative report. *Biol Psychiatry* 1990;27:923–926.
87. Roy A, DeJong J, Ferraro T, et al. CSF GABA and neuropeptides in pathological gamblers and normal controls. *Psychiatry Res* 1989;30:137–144.
88. Roy A, Pickar D, Gold P, et al. Diazepam-binding inhibitor and corticotropin-releasing hormone in cerebrospinal fluid. *Acta Psychiatr Scand* 1989;80:287–291.
89. Nordin C, Eklundh T. Lower CSF taurine levels in male pathological gamblers than in healthy controls. *Hum Psychopharmacol* 1996;11:401–403.
90. Koepp MJ, Gunn RN, Lawrence AD, et al. Evidence for striatal dopamine release during a video game. *Nature* 1998;393: 266–268.
91. Goyer PF, Semple WE, Rugle L, et al. Brain blood flow and dopamine receptor PET imaging in pathological gamblers. National Conference on Problem Gambling. Detroit: 1999.
92. Nyberg S, Eriksson B, Oxenstierna G, et al. Suggested minimal effective dose of risperidone based on PET-measured D2 and 5–HT2A receptor occupancy in schizophrenic patients. *Am J Psychiatry* 1999;156:869–875.
93. Botvinick M, Nystrom LE, Fissell K, et al. Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* 1999;402:179–181.
94. Childress AR, Mozely PD, McElgin W, et al. Limbic activation during cue-induced cocaine craving. *Am J Psychiatry* 1999;156: 11–18.
95. Volkow ND, Wang G-J, Fowler JS, et al. Association of methylphenidate-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers. *Am J Psychiatry* 1999; 156:19–26.
96. Lambert C. Deep cravings. *Harvard Mag* 2000;102:60–68.
97. Potenza MN, Armentano CJ, Steinberg MA, et al. An fMRI study of gambling urges in individuals with pathological gambling. World Congress of Biological Psychiatry Convention. Berlin: 2001.
98. Bechara A, Damasio AR, Damasio H, et al. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 1994;50:7–15.
99. Bechara A, Damasio H, Tranel D, et al. Deciding advantageously before knowing the advantageous strategy [see Comments]. *Science* 1997;275:1293–1295.
100. Bechara A, Damasio H, Tranel D, et al. Dissociation of working memory from decision making within the human prefrontal cortex. *J Neurosci* 1998;18:428–437.
101. Bechara A, Damasio H, Damasio HR, et al. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *J Neurosci* 1999;19:5473–5481.
102. Bechara A, Damasio H, Damasio HR. Emotion, decision making and the orbitofrontal cortex. *Cereb Cortex* 2000;10: 295–307.
103. Kaiser E, Johnson D, Hommer D. Alcoholics show impaired decision making on the Iowa Gambling Task. In: *Society for Neuroscience Annual Convention.* Miami Beach, FL: Society for Neuroscience, 1999.
104. Bechara A, Dolan S, Hindes A, et al. Decision-making deficits, linked to a dysfunctional orbitofrontal cortex, revealed in alcohol and stimulant abusers. *Society for Neuroscience Annual Convention.* Miami Beach, FL: Society for Neuroscience, 1999.
105. Grant SJ, Contoreggi CC, London ED. Drug abusers show impaired performance in a laboratory test of decision making. *Neuropsychologia* 2000;38(8):1180–1187.
106. London ED, Ernst M, Grant S, et al. Orbitofrontal cortex and human drug abuse: functional imaging. *Cereb Cortex* 2000;10: 334–342.
107. Eisen SA, Lin N, Lyons MJ, et al. Familial influences on gambling behavior: an analysis of 3359 twin pairs. *Addiction* 1998; 93:1375–1384.
108. Winters KC, Rich T. A twin study of adult gambling behavior. *J Gambling Stud* 1998;14:213–225.
109. Tsuang M, Lyons MJ, Eisen SA, et al. Genetic influences on DSM-III-R drug abuse and dependence: a study of 3,372 twin pairs. *Am J Med Genet* 1996;67:473–477.
110. Comings DE, Rosenthal RJ, Lesieur HR, et al. A study of the dopamine D2 receptor gene in pathological gambling. *Pharmacogenetics* 1996;6:223–234.
111. Comings DE, Gade R, Wu S, et al. Studies of the potential role of the dopamine D1 receptor gene in addictive behaviors. *Mol Psychiatry* 1997;2:44–56.
112. Comings DE. The molecular genetics of pathological gambling. *CNS Spectrums* 1998;3:20–37.
113. Perez de Castro I, Ibanez A, Torres P, et al. Genetic association study between pathological gambling and a functional DNA polymorphism at the D4 receptor gene. *Pharmacogenetics* 1997; 7:345–348.
114. Perez de Castro I, Ibanez A, Saiz-Ruiz J, et al. Genetic contribution to pathological gambling: possible association between a DNA polymorphism at the serotonin transpoter gene (5HTT) and affected men. *Pharmacogenetics* 1999;9:397–400.
115. Comings DE, Gonzalez N, Wu S, et al. Studies of the 48 bp repeat polymorphism of the DRD4 gene in impulsive, compulsive, addictive behaviors: Tourette syndrome, ADHD, pathological gambling, and substance abuse. *Am J Hum Genet* 1999; 88:358–368.
116. Blum K, Sheridan PJ, Wood RC, et al. Dopamine D2 receptor gene variants: association and linkage studies studies in impulsive-addictive-compulsive behavior. *Pharmacogenetics* 1995;5: 121–141.
117. Blum K, Cull JG, Braverman ER, et al. Reward deficiency syndrome. *Am Scientist* 1996;84:132–145.
118. Self DW, Barnhart WJ, Lehman DA, et al. Opposite modulation of cocaine-seeking behavior by D1– and D2–like dopamine receptor agonists. *Science* 1996;271:1586–1589.
119. Benjamin J, Patterson C, Greenber BD, et al. Population and familial association between the D4 dopamine receptor and measures of novelty seeking. *Nat Genet* 1996;12:81–84.
120. Ebstein RP, Novick O, Umansky R, et al. Dopamine D4 receptor (DRD4) exon III polymorphism associated with the human personality trait of novelty seeking. *Nat Genet* 1996;12:78–80.
121. Malhotra AK, Virkunnen M, Rooney W, et al. The association between the dopamine D4 (D4DR) 16 amino acid repeat and novelty seeking. *Mol Psychiatry* 1996;1:388–391.
122. Gelernter J, Kranzler H, Coccaro E, et al. D4 dopamine-receptor (DRD4) alleles and novelty-seeking in substance-dependent,

personality-disorder and control subjects. *Am J Hum Genet* 1997;61:1144–1152.
123. Jonssen EG, Nothen MM, Gustavson JP, et al. Lack of evidence for allelic association between personality traits and the dopamine D4 receptor gene polymorphisms. *Am J Psychiatry* 1997; 154:697–699.
124. Sullivan PF, Fifield WJ, Kennedy MA, et al. No association between novelty seeking and the type 4 dopamine receptor gene (DRD4) in two New Zealand samples. *Am J Psychiatry* 1998; 155:98–101.
125. Van Tol HH, Wu CM, Guan HC, et al. Multiple dopamine D4 receptor variants in the human population. *Nature* 1992; 358:149–152.
126. Heils A, Teufel A, Petri S, et al. Allelic variation of human serotonin transporter gene expression. *J Neurochem* 1996;66: 2621–2624.
127. Lesch KP, Bengal D, Heils A, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 1996;274:1527–1531.
128. Collier DA, Stober G, Li T, et al. A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. *Mol Psychiatry* 1996;1:453–460.
129. Ibanez A, Saiz-Ruiz J, Perez De Castro I, et al. Is serotonin transporter gene associated with pathological gambling? American Psychiatric Association Annual Convention. Toronto: American Psychiatric Association, 1998.
130. McConaghy N, Blaszczynski A, Frankova A. Comparison of imaginal desensitisation with other behavioural treatments of pathological gambling: a two- to nine-year follow-up. *Br J Psychiatry* 1991;159:390–393.
131. McConaghy N, Armstrong MS, Blaszczynski A, et al. Controlled comparison of aversive therapy and imaginal desensitization in compulsive gambling. *Br J Psychiatry* 1983;142: 366–372.
132. Petry NM, Armentano C. Prevalence, assessment, and treatment of pathological gambling: a review. *Psychiatr Serv* 1999; 50:1021–1027.
133. Stewart RM, Brown RI. An outcome study of Gamblers Anonymous. *Br J Psychiatry* 1988;152:284–288.
134. Bujold A, Ladouceur R, Sylvain C, et al. Treatment of pathological gamblers: an experimental study. *J Behav Ther Exp Psychiatry* 1994;25:275–282.
135. Sylvain C, Ladouceur R, Boisvert JM. Cognitive and behavioral treatment of pathological gambling: a controlled study. *J Consult Clin Psychol* 1997;65:727–732.
136. Price LH, Charney DS, Delgado PL, et al. Lithium and serotonin function: implications for the serotonin hypothesis of depression. *Psychopharmacology (Berl)* 1990;100:3–12.
137. Moskowitz JA. Lithium and lady luck: use of lithium carbonate in compulsive gambling. *NY State J Med* 1980;80:785–788.
138. Haller R, Hinterhuber H. Treatment of pathological gambling with carbamazepine. *Pharmacopsychiatry* 1994;27:129.
139. Goodman WK, Price LH, Rasmussen SA, et al. Efficacy of fluvoxamine in obsessive-compulsive disorder: a double-blind comparison with placebo. *Arch Gen Psychiatry* 1989;46:36–43.
140. Hollander E, Frenkel M, Decaria C, et al. Treatment of pathological gambling with clomipramine [Letter]. *Am J Psychiatry* 1992;149:710–711.
141. Hollander E, DeCaria C, Mari E, et al. Short-term single-blind fluvoxamine treatment of pathological gambling. *Am J Psychiatry* 1998;155:1781–1783.
142. Hollander E, DeCaria CM, Finkell JN, et al. A randomized double-blind fluvoxamine/placebo crossover trial in pathological gambling. *Biol Psychiatry* 2000;47:813–817.
143. Blanco-Jerez C, Petkova E, Ibanez A, et al. A long-term, double-blind, placebo-controlled study of fluvoxamine for pathological gambling. In: *American Psychiatric Association Annual Convention.* Washington, DC: American Psychiatric Association, 1999.
144. De La Gandara JJ, Sanz O, Gilaberte I. Fluoxetine: open-trial in pathological gambling. In: *American Psychiatric Association Annual Convention.* Washington, DC: American Psychiatric Association, 1999.
145. Kim SW, unpublished data, 2000.
146. O'Malley SS, Jaffe AJ, Chang G, et al. Naltrexone and coping skills therapy for alcohol dependence: a controlled study. *Arch Gen Psychiatry* 1992;49:881–887.
147. Volpicelli JR, Alterman AI, Hayashida M, et al. Naltrexone in the treatment of alcohol dependence [see Comments]. *Arch Gen Psychiatry* 1992;49:876–880.
148. Volpicelli JR, Watson NT, King AC, et al. Effect of naltrexone on alcohol "high" in alcoholics. *Am J Psychiatry* 1995;152: 613–615.
149. Barrett RP, Feinstein C, Hole WT. Effects of naloxone and naltrexone on self-injury: a double-blind, placebo-controlled analysis. *Am J Ment Retard* 1989;93:644–651.
150. Walters AS, Barrett RP, Feinstein C, et al. A case report of naltrexone treatment of self-injury and social withdrawal in autism. *J Autism Dev Disord* 1990;20:169–176.
151. Roth AS, Ostroff RB, Hoffman RE. Naltrexone as a treatment for repetitive self-injurious behaviour: an open-label trial. *J Clin Psychiatry* 1996;57:233–237.
152. Kim SW. Opioid antagonists in the treatment of impulse-control disorders. *J Clin Psychiatry* 1998;59:159–164.
153. Crockford DN, el-Guebaly N. Naltrexone in the treatment of pathological gambling and alcohol dependence [Letter]. *Can J Psychiatry* 1998;43:86.
154. Kraeplin E. *Psychiatrie.* Leipzig, Germany: Verlag Von Johann Ambrosius Barth, 1915:408–409.
155. Bleuler E. *Textbook of psychiatry.* 1924, New York: Macmillan, 1924:540.
156. Christenson GA, Faber RJ, de Zwaan M, et al. Compulsive buying: descriptive characteristics and psychiatric comorbidity. *J Clin Psychiatry* 1994;55:5–11.
157. McElroy SL, Keck PE, Pope HG Jr, et al. Compulsive buying: a report of 20 cases. *J Clin Psychiatry* 1994;55:242–248.
158. Lejoyeaux M, Ades J, Tassain V, et al. Phenomenology and psychopathology of uncontrolled buying. *Am J Psychiatry* 1996; 153:1524–1529.
159. Black DW, Repertinger S, Gaffney GR, et al. Family history and psychiatric comorbidity in persons with compulsive buying: preliminary findings. *Am J Psychiatry* 1998;155:960–963.
160. Faber RJ, O'Guinn TC. A clinical screener for compulsive buying. *J Consumer Res* 1992;19:459–469.
161. Schlosser S, Black DW, Repertinger S, et al. Compulsive buying: demography, phenomenology and comorbidity in 46 subjects. *Gen Hosp Psychiatry* 1994;16:205–212.
162. Lejoyeaux M, Hourtane M, Ades J. Compulsive buying and depression. *J Clin Psychiatry* 1995;56:38.
163. Lejoyeaux M, Tassain V, Solomon J, et al. Study of compulsive buying in depressed patients. *J Clin Psychiatry* 1997;58: 169–173.
164. McElroy SL, Satlin A, Pope HG Jr, et al. Treatment of compulsive shopping with antidepressants: a report of three cases. *Ann Clin Psychiatry* 1991;3:199–204.
165. Black DW, Monahan P, Gabel J. Fluvoxamine in the treatment of compulsive buying. *J Clin Psychiatry* 1997;58:159–163.
166. Coleman E. Sexual compulsivity: definition, etiology, and treatment considerations. In: Coleman E, ed. *Chemical dependency and intimacy dysfunction.* New York: Hawarth, 1987.
167. Black DW. The epidemiology and phenomenology of compulsive sexual behavior. *CNS Spectrums* 2000;5:26–35.

168. Coleman E. Is your patient suffering from compulsive sexual behavior? *Psychiatr Ann* 1992;22:320–325.
169. Carnes P. *Don't call it love: recovery for sexual addiction.* New York: Bantam Books, 1991.
170. Carnes PJ, Delmonico DL. Childhood abuse and multiple addictions: research findings in identified sexual addicts. *Sex Addict Compuls* 1996;3:258–268.
171. Schneider JP, Schneider BH. Couple recovery from sexual addiction/coaddiction: results of a survey of 88 marriages. *Sex Addict Compuls* 1996;3:111–126.
172. Kafka MP, Prentky R. Fluoxetine treatment of nonparaphilic sexual addictions and paraphilias in men. *J Clin Psychiatry* 1992; 53:351–358.
173. Eyres A. Transvestism: employment of somatic therapy with subsequent improvement. *Dis Nerv Syst* 1960;21(1):52–53.
174. Bartova D, Nahunek K, Svetske J. Pharmacological treatment of deviant sexual behavior. *Activ Nerv Sup (Praha)* 1978;20: 72–74.
175. Ward NG. Successful lithium treatment of transvestitism associated with manic-depression. *J Nerv Ment Dis* 1975;161: 204–206.
176. Cesnik JA, Coleman E. Use of lithium carbonate in the treatment of autoerotic asphyxia. *Am J Psychother* 1989;63:277–286.
177. Federoff JP. Buspirone hydrochloride in the treatment of transvestic fetishism. *J Clin Psychiatry* 1988;49:408–409.
178. Kafka MP. Successful antidepressant treatment of nonparaphilic sexual addictions and paraphilias in men. *J Clin Psychiatry* 1991; 52:60–65.
179. Snaith RP. Five exhibitionists and a method of treatment. *Br J Psychiatry* 1981;132:126–130.
180. Kruesi MJP, Fine S, Valladares L, et al. Paraphilias: a double-blind crossover comparison of clomipramine vs. desipramine. *Arch Sex Behav* 1993;21:587–593.
181. Federoff JP. Serotonergic drug treatment of deviant sexual interests. *Ann Sex Res* 1993;6:105–121.
182. Greenberg DM, Bradford JMW. Treatment of the paraphilic disorders: a review of the role of the selective serotonin reuptake inhibitors. *Sex Abuse J Treat Res* 1997;9:349–360.
183. Kafka MP. Sertraline pharmacotherapy for paraphilias and paraphilia-related disorders: an open trial. *Ann Clin Psychiatry* 1994; 6:189–195.
184. Perilstein RD, Lipper S, Friedman LJ. Three cases of paraphilias responsive to fluoxetine treatment. *J Clin Psychiatry* 1991;52: 169–170.
185. Bradford JMW. An open pilot study of sertraline in the treatment of outpatients with pedophilia. In: *American Psychiatric Association Annual Convention.* Washington, DC: American Psychiatric Association, 1995.
186. Greenberg DM, Bradford JMW, Curry S, et al. A comparison of treatment of paraphilias with three serotonin reuptake inhibitors: a retrospective study. *Bull Am Acad Psychiatry Law* 1996; 24:525–532.
187. Kafka MP. Psychopharmacologic treatments for nonparaphilic compulsive sexual behaviors. *CNS Spectrums* 2000;5:49–59.
188. Meyer WI, Cole C, Emory E. Depo provera treatment for sex offending behavior: an evaluation of outcome. *Bull Am Acad Psychiatry Law* 1992;20:249–259.
189. Gottesman HG, Schubert DSP. Low-dose oral medroxyprogesterone acetate in the management of the paraphilias. *J Clin Psychiatry* 1993;54:182–188.
190. Bradford JMW, Pawlak A. Double-blind placebo crossover study of cyproterone acetate in the treatment of the paraphilias. *Arch Sex Behav* 1993;22:383–403.
191. Rosler A, Witzum E. Treatment of men with paraphilia with a long-acting analogue of gonadotropin-releasing hormone. *N Engl J Med* 1998;338:416–422.
192. Levitsky AM, Owens NJ. Pharmacologic treatment of hypersexuality and paraphilias in nursing home residents. *J Am Geriatr Soc* 1999;47:231–234.
193. Grossman LS, Martis B, Fichtner CG. Are sex offenders treatable? A research overview. *Psychiatr Serv* 1999;50:349–361.
194. Cooper AJ, Sandhu S, Losztyn S, et al. A double-blind placebo-controlled trial of medroxyprogesterone acetate and cyproterone acetate with seven pedophiles. *Can J Psychiatry* 1992;37: 687–693.
195. Kiersch T. Treatment of sex offenders with Depo-provera. *Bull Am Acad Psychiatry Law* 1990;18:179–187.
196. Dickey R. The management of a case of treatment-resistant paraphilia with a long-acting LHRH agonist. *J Clin Psychiatry* 1992;37:567–569.
197. Kyomen HH, Satlin A, Hennen J, et al. Estrogen therapy and aggressive behavior in elderly patients with moderate-to-severe dementia: results from a short-term, randomized, double-blind trial. *Am J Geriatr Psychiatry* 1999;7:339–348.
198. Lothstein LM, Fogg-Waberski, J, Reynolds P. Risk management of sexual disinhibition in geriatric patients. *Conn Med* 1997; 61:609–618.
199. Young KS. Pathological Internet use: the emergence of a new clinical disorder. American Psychological Association Annual Convention. Toronto: American Psychological Association, 1996.
200. Young KS. Psychology of computer use. XL. Addictive use of the Internet: a case that breaks the stereotype. *Psychol Rep* 1996; 79:899–902.
201. Belsare TJ, Gaffney GR, Black DW. Compulsive computer use. *Am J Psychiatry* 1997;154:289.
202. Young KS. Internet addiction: what makes computer-mediated communication habit-forming? American Psychological Association Annual Convention. Chicago: American Psychological Association, 1997.
203. Griffiths MD. Internet addiction: does it really exist? In: Gackenbach J, ed. *Psychology and the Internet: intrapersonal, interpersonal, and transpersonal implications.* New York: Academic, 1998:61–75.
204. Fearing JD. Computer addiction: "hooked on the Net." *www.nationalcounseling.com/cmpadict.html* 2000.
205. Pratarelli ME, Browne BE, Johnson K. The bits and bytes of computer/Internet addiction: a factor analytic approach. *Behav Res Methods Instr Comput* 1999;31:305–314.
206. Black DW, Belsare G, Schlosser S. Clinical features, psychiatric comorbidity, and health-related quality of life in persons reporting compulsive computer use behavior. *J Clin Psychiatry* 1999; 60:839–844.
207. Cooper A, Delmonico DL, Burg R. Cybersex users, abusers, and compulsives: new findings and implications. Sexual Addiction and Compulsion 2000;7(1–2):5–29.