# The relationship between impulse-control disorders and obsessive–compulsive disorder: A current understanding and future research directions

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## ABSTRACT

Impulse-control disorders (ICDs) constitute a heterogeneous group of conditions linked diagnostically by difficulties in resisting "the impulse, drive, or temptation to perform an act that is harmful to the person or to others." Specific ICDs share clinical, phenomenological and biological features with obsessive–compulsive disorder (OCD) that have suggested that these disorders might be categorized together. However, other data suggest significant differences between OCD and ICDs. In this article, clinical, phenomenological and biological features of the formal ICDs are reviewed and compared and contrasted with those of OCD. Available data indicate substantial differences between ICDs and OCD that suggest independent categorizations. Existing research gaps are identified and avenues for future research suggested.

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## 1. Introduction

In anticipation of the generation of the next editions of the Diagnostic and Statistical Manual and the International Classification of Diseases, the American Psychiatric Association, National Institutes of Health and World Health Organization have sponsored a series of meetings entitled, "The Future of Psychiatric Diagnosis: Refining the Research Agenda." The conference focusing on Obsessive-Compulsive Spectrum Disorders was convened on June 20–22, 2006. Among the topics discussed were which disorders should be considered within the obsessive–compulsive (OC) spectrum and whether disorders currently classified elsewhere might be alternatively grouped in a manner supported by empirical data. Among the disorders warranting consideration for grouping within an OC spectrum were the impulse-control disorders (ICDs), including pathological gambling (PG) and intermittent explosive disorder (IED). Multiple domains representing potential endophenotypes were identified prior to the meeting to foster exploration and discussion of this topic. These domains included phenomenology, co-morbidity, course of illness, family history, genetics, brain circuitry, cross-species considerations, pharmacology, treatments and interventions, and cultural influences.

### 1.1. Impulse-control disorders (ICDs): current categorization in DSM-IV-TR

ICDs are currently classified within the DSM-IV-TR in the category of "Impulse Control Disorders Not Elsewhere Classified" (American Psychiatric Association Committee on Nomenclature and Statistics, 2000). As the category name implies, other disorders characterized by impaired impulse control (e.g., substance abuse and dependence, cluster B personality disorders, and eating disorders) are categorized elsewhere in the DSM-IV-TR. Included in the formal ICD category are IED, kleptomania, pyromania, PG, trichotillomania, and ICD not otherwise specified (NOS). Whereas formal criteria for other ICDs have been proposed [e.g., for excessive, problematic or compulsive behavior in the domains of shopping or buying, computer or internet use, sex, and skin picking (McElroy et al., 1994; Lejoyeaux et al., 1996; Potenza and Hollander, 2002; Grant and Potenza, 2004; Koran et al., 2006; Liu and Potenza, 2007)], clinically significant behaviors in these areas would currently be diagnosed as ICDs NOS. This article will focus

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on those ICDs with specific diagnostic criteria already defined in the DSM since the ICDs without clearly defined diagnostic criteria have been less studied.

## 1.2. Common features of ICDs: relationship to OCD

As described in the DSM-IV-TR, the essential feature of ICDs is "the failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others." Each ICD is characterized by a recurrent pattern of behavior that has this essential feature within a specific domain. The repetitive engagement in these behaviors ultimately interferes with functioning in other domains. In this respect, ICDs resemble OCD. That is, individuals with OCD often report difficulties resisting the urge to engage in specific behaviors (e.g., cleaning, ordering or other ritualistic behaviors) that interfere with functioning. However, this resemblance is not unique to OCD. For example, individuals with drug addictions often report difficulty in resisting the urge to use drugs. Perhaps for these reasons, two of the most common conceptualizations of ICDs link them to an OC spectrum or to addictive disorders (Hollander and Wong, 1995; Potenza et al., 2001a,b). Although the categorizations of ICDs as OC-spectrum or addictive disorders are not mutually exclusive, they have important theoretical and clinical implications given differences in the prevention and treatment strategies for these disorders (Tamminga and Nestler, 2006). Heterogeneities in OCD and addictions and changes that occur during the course of these disorders complicate comparisons across disorders, particularly as investigations concurrently examining OCD, substance addictions, and ICDs are scarce.

ICDs and OCD have been conceptualized to lie along an impulsive/compulsive spectrum with disorders with high harm avoidance like OCD positioned closer to the more compulsive end and those with low harm avoidance like many ICDs positioned closer to the more impulsive end (Hollander and Wong, 1995). Although data indicate that individuals with OCD score high on measures of harm avoidance and those with ICDs like PG score high on measures of impulsivity and related measures like novelty seeking (Potenza, 2007), recent data suggest a more complex relationship between impulsivity and compulsivity as they relate to OCD and ICDs. For example, individuals with OCD as compared to control subjects demonstrated high levels of cognitive impulsiveness (Ettelt et al., 2007). An association between measures of cognitive impulsiveness and aggressive obsessions and checking suggests that impulsiveness may be particularly relevant to specific sub-groups of individuals with OCD (Ettelt et al., 2007). Another study of OCD, PG and control subjects found that the majority of both PG and OCD subjects were characterized by high levels of both impulsivity and harm avoidance, suggesting a more complex relationship between impulsivity and compulsivity than originally proposed (Potenza, 2007). More research is needed to examine the extent to which some of these similarities across these disorders might explain similarities in specific clinical phenomena; e.g., whether high levels of impulsiveness in PG and OCD account for high levels of suicidality reported across these disorders (Ledgerwood et al., 2005; Torres et al., 2006). Furthermore, the complex relationship between impulsivity may be influenced by different factors in specific populations. For example, gender differences in the relationship between measures of impulsivity and compulsivity have been reported in a sample of high school students (Li and Chen, 2007), and the extent to which these findings extend to groups with OCD and/or ICDs has yet to be systematically investigated.

As described in the DSM-IV-TR (American Psychiatric Association Committee on Nomenclature and Statistics, 2000), additional features common to ICDs are feelings of "tension or arousal before committing the act" and "pleasure, gratification or relief at the time of committing the act." There may or may not be feelings of regret, self-reproach or guilt following the act. In multiple respects, the motivations and sensations preceding and relating to the repetitive acts in ICDs and OCD are different. Among the most striking differences is the ego-dystonic nature typically ascribed to the obsessions and compulsions in OCD as compared with the ego-syntonic feelings typically associated with ICD behaviors such as gambling (Stein and Lochner, 2006). The ego-syntonic nature of ICD behaviors is at least superficially more similar to the experience of drug use behaviors in drug dependence. Similarly, the variability in the degree of guilt or remorse following the ICD behavior is reminiscent of the variability observed in individuals with drug addictions. However, the motivational and emotional processes underlying engagement in and experiencing of the repetitive behaviors in ICDs may change over time (Chambers et al., 2007; Brewer and Potenza, 2008). For example, individuals with PG often report that while they initially gambled to win money, later they became motivated simply by the experience of gambling itself (to be "in action"). Whereas gambling urges early in the course of PG are typically pleasurable, over time they often become less ego-syntonic as people more fully appreciate the negative consequences of their gambling and struggle to refrain. Although these changes appear similar to those reported during the course of the addictive process, they also resemble processes in OCD. That is, as the urge to engage in an ICD behavior and the behavior itself become more ego-dystonic, less driven by seeking of pleasure and more driven by a desire to reduce an anxious or distressing state, the urge and behavior more closely resemble the phenomenological features of obsessions and compulsions, respectively, in OCD. On the other hand, the ego-dystonic quality of OCD symptoms may diminish over time (Rasmussen and Eisen, 1992).

## 1.3. Heterogeneity of ICDs: unique features

The behavioral domains covered by the current ICDs include anger management, stealing, fire-setting, gambling and hair-pulling. Since these domains are in many ways distinct and disparate, a question arises as to whether the disorders should be grouped together. The DSM-IV-TR groups some other disorders characterized by excessive or interfering levels of engagement separately according to the specific target behavior (e.g., substance-related and eating disorders). Data examining the extent to which ICDs warrant clustering are sparse. Until recently, ICDs were typically omitted from large, epidemiological studies. Although recent studies like the National Epidemiologic Survey on Alcoholism and Related Conditions (NESARC) and the National Co-morbidity Survey Replication Study (NCS-R) included measures of specific ICDs like PG and IED (Petry et al., 2005; Kessler et al., 2006), the entire group of disorders has not been assessed concurrently in a large, population-based sample. Thus, the extent to which they form a cohesive group has not been directly examined, nor has the extent to which they fit into an empirically supported structure of psychiatric disorders. That is, data indicate that most psychiatric disorders can be categorized into internalizing or externalizing clusters (Krueger, 1999; Kendler et al., 2003). Although ICDs often share with externalizing disorders a disinhibited personality style or a lack of constraint (Slutske et al., 2000; Slutske et al., 2001; Slutske et al., 2005), they also share features with internalizing disorders such as major depression (Potenza et al., 2005; Potenza, 2007). Where OCD and ICDs best fit within this structure warrants direct investigation. Whereas the disabling distress and anxiety associated with OCD contribute to its current classification in DSM-IV-TR as an anxiety disorder, it is categorized separately in the 10th edition of the International Classification of Diseases (World Health Organization, 2003).

Existing studies suggest that the ICDs represent a heterogeneous group of disorders. Within a clinical sample of subjects with OCD, pathological skin-picking and nail-biting were frequently endorsed and other ICDs were relatively uncommon (Grant et al., 2006a). OCD subjects with ICDs were more likely than those without OCD to acknowledge hoarding and symmetry obsessions and hoarding and repeating rituals, suggesting a differential association of ICDs with

sub-groups of individuals with OCD (Grant et al., 2006a). Within a sample of probands with or without OCD, excessive "grooming disorders" including trichotillomania and pathological nail-biting and skin-picking were more common in the individuals with OCD (Bienvenu et al., 2000). In contrast, other ICDs, including PG, pyromania and kleptomania, were not more commonly identified in individuals with OCD versus those without the disorder. This pattern extended to first-degree relatives, suggesting a heritable component to the overlap between OCD and the grooming-related ICD behaviors. However, a study of individuals with trichotillomania and their family members did not find a close link between OCD and trichotillomania (Lenane et al., 1992). Methodological limitations, including relatively small sample sizes, might be responsible in part for the heterogeneity in findings. Co-occurring ICDs in OCD have been associated with an earlier age at onset of OCD, a more insidious appearance of OC symptoms, a greater number and severity of OC symptoms, and a larger number of therapeutic trials (du Toit et al., 2005; Fontenelle et al., 2005; Matsunaga et al., 2005; Grant et al., 2006a).

An independent study found that OC-spectrum disorders (including ICDs) in subjects with OCD clustered into the following three groups: 1) a "reward deficiency" group that included trichotillomania, PG, Tourette's disorder, and hypersexual disorder; 2) an "impulsivity" group that included kleptomania, IED, compulsive shopping and self-injurious behaviors; and 3) a "somatic" group that included body dysmorphic disorder and hypochondriasis (Lochner et al., 2005). The different clusters correlated with different clinical features of the OCD sample. Specifically, cluster 1 was associated with early age at onset of OCD and the presence of tics, cluster 2 with female gender and childhood trauma, and cluster 3 with poor insight. These findings highlight several important points. First, they suggest that ICDs cluster into distinct groups, particularly within subjects with OCD. Second, specific groups of ICDs might be particularly relevant to specific subsets of individuals with OCD. That is, data support the existence of multiple sub-types of OCD with different clinical characteristics and treatment responses [e.g., tic vs. non-tic-related and the relationship to early onset and treatment refractoriness (Leckman et al., 1994; McDougle et al., 1994; Denys et al., 2003; Leckman et al., 2003; Rosario-Campos et al., 2005)]. Factor-analytic studies have suggested that particular OCD symptom types (aggressive obsessions/checking; religious or sexual obsessions; symmetry/ordering; contamination/cleaning; hoarding) may represent biologically distinct disorders (Leckman et al., 2001), and positron emission tomography (PET) studies have found differences in OCD subjects with different symptom clusters (Rauch et al., 1998). Specific ICDs (or clusters thereof) may be particularly relevant to specific sub-types of OCD; e.g., IED and aggressive sub-types of OCD. More research is needed to examine the specific categorical and dimensional features of OCD in relation to ICDs in order to clarify these relationships (Lochner and Stein, 2006; Stein and Lochner, 2006).

*1.4. Individual ICDs*

Given individual differences between the ICDs, representative ICDs were selected for further consideration according to the potential endophenotype domains identified for the OC-spectrum workgroup meeting: 1) phenomenology and epidemiology; 2) co-occurring disorders; 3) family history and genetics; 4) neurobiology, including animal models and human studies; 5) pharmacological and behavioral treatments and interventions; and 6) cultural considerations. Some aspects relevant to OCD [e.g., important immune system contributions to OCD in a subset of individuals (Snider and Swedo, 2004)] are not presently suspected in the etiology of any of the formal ICDs and are not discussed below. Two ICDs, IED and PG, were selected for consideration here because they 1) have been identified as belonging to distinct categories in OCD subjects in a data-driven cluster analysis (Lochner et al., 2005); and 2) have been most

thoroughly studied to date. This latter aspect is particularly relevant in that not all ICDs have sufficient empirical data to address adequately all of the domains specified by the OC Spectrum Disorders DSM V Research workgroup. The third cluster of OC-spectrum disorders previously identified [the somatic cluster including body dysmorphic disorder (Lochner et al., 2005)] will not be addressed here because it does not include formal ICDs and is covered in a separate article derived from the OC-spectrum workgroup meeting. The findings from the cluster analysis (Lochner et al., 2005) have limitations; e.g., they are obtained from a population with OCD, thereby potentially introducing bias. However, similar studies have not been performed in other populations. Consequently, these data seem the best available to guide decision-making regarding which ICDs to cover most extensively here. Although it would be desirable to cover each ICD in similar detail in the following sections, space limitations coupled with the intent to cover adequately the domains identified prevent this.

## 2. Intermittent explosive disorder (IED)

*2.1. Phenomenology and epidemiology*

Available data suggest that although there are similarities between IED and OCD, substantial differences exist. IED is characterized by recurrent episodes of aggression that are out of proportion to psychosocial stressors and/or provocation and are not better accounted for by another mental disorder, by comorbid medical conditions, or by the physiological effects of a drug or other substance with psychotropic properties (American Psychiatric Association Committee on Nomenclature and Statistics, 2000). IED may be repetitive, intrusive, persistent and recurrent like OCD, but it is often episodic. Unlike compulsions in OCD, aggressive outbursts in IED typically do not occur in response to an obsession. Aggression is typically unplanned and occurs without substantial forethought (Grant and Potenza, 2006a). Aggression in IED differs from compulsions in OCD in that it may be gratifying and accompanied by excitement rather than by anxiety reduction; however, like OCD compulsions, aggressive acts can be perceived as distressing (McElroy et al., 1998).

Chart reviews of psychiatric inpatients (Monopolis and Lion, 1983) and clinical interviews (Felthous et al., 1991) reported prevalence estimates of IED from 1% to 3% in psychiatric settings (Olvera, 2002). A more recent study of adult psychiatric inpatients found that 6.4% and 6.9% had current and lifetime IED, respectively (Grant et al., 2005). A separate study of adolescent psychiatric inpatients found a larger proportion of subjects (12.7%) met criteria for IED (Grant et al., 2007). In both the adult and adolescent inpatient studies, diagnoses of IED were only identified following active screening and interviewing. These findings suggest that IED, like other ICDs, often goes undiagnosed and thus is often not targeted for treatment. Estimates of IED in community samples suggest that IED is common. For example, one community study found a 11.1% lifetime prevalence and a 3.2% 1-month prevalence (Cocarro et al., 2004). In the NCS-R study, lifetime and 12-month prevalence estimates of DSM-IV IED were 7.3% and 3.9%, respectively (Kessler et al., 2006). Together, these studies suggest that IED is more common than OCD.

In some respects, the clinical characteristics and course of IED resemble those of other disorders characterized by impaired control (e.g., substance use disorders) more than those of OCD. Unlike OCD, in which there is an approximately 1:1 male-to-female ratio (Robins and Regier, 1991) or a slight female predominance (Mohammadi et al., 2004; Grabe et al., 2006), IED is characterized by an approximately 2:1 male predominance (Grant and Potenza, 2006a; Kessler et al., 2006). Age at onset for DSM-IV IED peaks in the teenage years, is earlier for men than women, and is earlier than for most disorders that frequently co-occur with IED (see below), with the possible exception of phobic anxiety disorders (Kessler et al., 2006). Similarly, many individuals (49%) report OCD symptom onset during childhood or adolescence, and a majority (75%) report onset prior to age 25 (Robins

and Regier, 1991). In IED, aggressive behaviors occur in nearly all decades of life beginning in the first decade, peaking in the third decade, diminishing steadily after the fourth decade, and culminating in little or no reported aggression by the eighth decade (Cocarro et al., 2004). Sociodemographic correlates of lifetime IED include low educational level, being married, and having low family income (Kessler et al., 2006). In contrast, OCD does not show a clear association with educational level, and married individuals are less likely to be afflicted (Robins and Regier, 1991).

### 2.2. Co-occurring disorders

Like other ICDs (Potenza, 2007), IED frequently co-occurs with other psychiatric disorders including OCD. Initial findings were reported from clinical samples. One study reported OCD in 22% of individuals with IED (McElroy et al., 1998). Estimates of IED in clinical samples of subjects with OCD have ranged from about 2% to about 10% (du Toit et al., 2005; Fontenelle et al., 2005). In the NCS-R, the vast majority (81.8%) of patients with lifetime broadly defined IED met criteria for at least one other lifetime DSM-IV disorder (Kessler et al., 2006). A wide range of psychiatric disorders was found in association with IED including mood, anxiety, impulse control and substance use disorders (Kessler et al., 2006). Among individuals with broadly defined IED, 4.4% met criteria for OCD. The odds ratio (OR) for broadly defined IED in association with OCD was 2.5 [95% confidence interval (CI): 1.1–5.7]. Within the broadly defined group, there was no significant difference in the degree of association between the narrowly defined IED and OCD (OR: 1.1; 95% CI: 0.2–6.9). In contrast, generalized anxiety disorder, all ICDs and many substance use disorders showed significantly elevated ORs for both broadly and narrowly defined IED, suggesting a particularly close relationship between these disorders and both less and more severe forms of IED (Kessler et al., 2006).

### 2.3. Family history and genetics

Although studies suggest that impulsive and aggressive behaviors demonstrate familial transmission (Halperin et al., 2003; Kreek et al., 2005), few genetic or family history studies have been performed in individuals with IED. Several lines of research have identified familial sociopathy and aggression as salient risk factors for the persistence of childhood aggression into adolescence and adulthood (Cadoret et al., 1995; Frick et al., 1990). A familial pattern of aggressive behaviors has been associated with central serotonin function (see Section 2.4) (Halperin et al., 2003). The family history of individuals with IED is characterized by high rates of mood, substance use and other impulse-control disorders (McElroy et al., 1998). A genetic linkage study found an association between an allelic variant of the serotonin (5HT) 1B receptor gene and alcoholism in aggressive/impulsive individuals who met criteria either for antisocial personality disorder or IED (Lappalainen et al., 1998). In contrast, the 5HT 1B receptor has not been implicated in genetic studies of OCD, although several other 5HT-related genes (e.g., those encoding the 5HT 1D and 5HT 2A receptors and the 5HT transporter) have been implicated in some but not all studies of OCD (Hemmings and Stein, 2006).

### 2.4. Neurobiology: animal models and human studies

Many neurotransmitter systems and brain regions contribute to impulsive aggression. Animal models have implicated numerous biological systems and neurotransmitters including those involving testosterone, gamma-amino butyric acid, nitric oxide, monoamine oxidase, glutamate, dopamine and serotonin (Olivier and Young, 2002; Korff and Harvey, 2006). Within these systems, specific components seem particularly salient. For example, robust data implicate the 5HT 1B receptor in impulsive aggression in mice; knockout mice lacking the receptor show marked physical aggression

(Saudou et al., 1994). These findings are consistent with human studies implicating the receptor in impulsive-aggressive alcoholism (Lappalainen et al., 1998). Although some of the same systems (e.g., 5HT, dopamine) are relevant to both IED and OCD, they seem involved in different ways. For example, disruption of the genes encoding the 5HT 2C receptor and the dopamine transporter generates stereotypic behaviors resembling OCD (Korff and Harvey, 2006), as compared with the 5HT 1B receptor manipulation more relevant to IED. Genetic variations in commonly occurring 5HT-related gene variants (e.g., of the 5HT transporter) influence 5HT measures associated with impulsive aggression (Mannelli et al., 2006).

Few studies have examined the neurobiology of IED in humans, and those available have not consistently identified between-group differences. For example, a magnetic resonance spectroscopy study that identified differences in adolescent bipolar and control subjects in myo-inositol measures found no differences between adolescents with and without IED (Davanzo et al., 2003). Although few studies have been performed in individuals with IED, many have investigated individuals with impulsive aggression. Multiple biological systems, including those involving opiates, vasopressin, testosterone, catecholamines (norepinephrine, dopamine), and 5HT, have been identified as contributing to human aggression (Coccaro and Siever, 2002). Among the most widely replicated findings is that of low levels of central measures of 5HT (particularly of the 5HT metabolite 5-hydroxy indole acetic acid) in impulsive-aggressive individuals (Coccaro and Siever, 2002; Williams and Potenza, 2008). Although 5HT systems have been implicated in OCD, the nature of the involvement differs, as judged by the results of pharmacological challenge studies. Administration of the serotonergic drugs meta-chlorophenylpiperazine [m-CPP, a 5HT1 and 5HT2 receptor partial agonist (Potenza and Hollander, 2002)] and fenfluramine [a drug inducing 5HT release and having post-synaptic 5HT action (Curzon and Gibson, 1999)] is associated with an exacerbation of OC symptoms and enhanced prolactin release in subjects with OCD (Hollander et al., 1991; Monteleone et al., 1997; Gross-Isseroff et al., 2004). However, groups of children and adults characterized by impulsive aggression exhibit a blunted prolactin response to m-CPP and fenfluramine (Cocarro et al., 1997; Halperin et al., 2003; New et al., 2004b; Patkar et al., 2006). These findings are consistent with those from primates, in which an inverse relationship between aggression and serotonergic activity has been reported (Tiefenbacher et al., 2003).

Brain imaging studies have yielded insight into the pathophysiology of impulsive aggression in humans. Consistent with a role for the ventromedial prefrontal cortex [vmPFC, a region including the medial orbital frontal cortex (Bechara, 2003)] in decision-making and social and moral judgments (Damasio, 1994; Anderson et al., 1999; Bechara, 2003), individuals with impulsive aggression show relatively diminished activation of the vmPFC. For example, among individuals with depression, those with anger attacks showed an inverse correlation between regional cerebral blood flow in the left vmPFC and left amygdala during anger induction, whereas subjects without anger attacks did not (Dougherty et al., 2004). Aspects of vmPFC function as related to impulsive aggression appear linked to 5HT function. Individuals with impulsive aggression as compared to those without show blunted hemodynamic responses to the serotonergic drugs fenfluramine (Siever et al., 1999) and m-CPP (New et al., 2002). Individuals with impulsive aggression also show diminished 5HT availability in the anterior cingulate cortex, including within the ventral portion included in the vmPFC (Frankle et al., 2005). The 5HT reuptake inhibitor (SRI) fluoxetine increases metabolism within orbitofrontal cortex (New et al., 2004a). Although orbitofrontal cortical function has been implicated in OCD, the nature of its involvement differs from that in impulsive aggression. Specifically, in apparent contrast to the diminished vmPFC activity associated with impulsive aggression, increased activation of cortical-striato-thalamo-cortical circuitry, including orbitofrontal regions involving the vmPFC, has been repeatedly implicated in OCD (Korff and Harvey, 2006;

Mataix-Cols and van den Heuvel, 2006). However, specific sub-groups of individuals with OCD show differential activation of this circuitry. For example, during an fMRI symptom provocation study, individuals with washing OCD showed strong activation of vmPFC and caudate, those with checking OCD showed strong activation of putamen/globus pallidus, thalamus, and dorsal cortical areas, and those with hoarding OCD showed strong activation of precentral gyrus and orbitofrontal cortex (Mataix-Cols et al., 2004).

### 2.5. Pharmacological and behavioral treatments and interventions

Relatively few clinical trials have investigated the efficacy and tolerability of drugs in the treatment of IED. Drugs that block serotonin transport (both relatively selective and non-selective SRIs like sertraline and venlafaxine, respectively) have been reported in case reports to be helpful in individuals with IED (McElroy et al., 1998; Feder, 1999). Although this finding may suggest similarities to the use of SRIs in treating OCD, the doses employed were often lower than those typically used in OCD (Denys, 2006). For example, in one case series involving IED subjects, sertraline was dosed at 50–100 mg/day (Feder, 1999) instead of at doses approaching 200 mg/day, as are often used for OCD. A role for SRIs in the treatment of IED is consistent with their efficacy in targeting impulsive aggression (Coccaro and Kavoussi, 1997; Reist et al., 2003). Mood stabilizing drugs like lithium and valproic acid have been reported helpful in open-label IED treatment studies (McElroy et al., 1998), consistent with findings from some but not all studies of these and other mood stabilizers (carbamazepine, phenytoin) in targeting impulsive aggression (Olvera, 2002; Dell'Osso et al., 2006; Grant and Potenza, 2006a). However, lithium lacks efficacy as an augmenting agent in the treatment of OCD (McDougle et al., 1991), although some antipsychotic drugs (e.g., olanzapine, risperidone) with mood stabilizing properties have demonstrated efficacy in augmenting SRI response in refractory OCD (Denys, 2006). Some antipsychotic drugs have also been effective in treating aggression in controlled studies (Findling et al., 2001; Buitelaar et al., 2001). Alpha-adrenergic agonists and beta-adrenergic antagonists have each shown some promise in targeting impulsive aggression (Olvera, 2002; Dell'Osso et al., 2006; Grant and Potenza, 2006a), whereas no role for these drugs has been demonstrated in the treatment of OCD (Denys, 2006). Taken together, although the data for IED are limited, existing information suggests that the similarities in the pharmacological treatments of IED and OCD are outweighed by substantial differences.

Data from psychotherapy trials for individuals with IED are limited, with suggestions that insight-oriented psychotherapy and behavioral therapy might be helpful for some individuals (Grant and Potenza, 2006a). Limited studies involving small numbers of subjects have not found significant improvement related to group, couples or family therapies (McElroy et al., 1998). With respect to aggressive behaviors, controlled studies of behavioral interventions including cognitive behavior therapy, group therapy, family therapy and social skill training report some effectiveness for aggressive patients (Alpert and Spilman, 1997). These treatments differ from the exposure and response prevention methods that are effective in the treatment of OCD (Neziroglu et al., 2006). Thus, like the pharmacotherapy data, the behavioral therapy findings suggest significant differences between IED and OCD.

### 2.6. Cultural considerations

Cultural attitudes towards aggressive behaviors warrant consideration in IED, although little systematic research has been performed with respect to the influence of cultural factors. One form of aggression, amok episodes, is characterized by acute, unrestrained violence, typically associated with amnesia, and traditionally seen only in southeastern Asian countries (American Psychiatric Association Committee on Nomenclature and Statistics, 2000). The extent to which IED resembles amok episodes or perceptions thereof warrants examination. Although OCD occurs across racial/ethnic groups and geographic locations (Karno et al., 1988; Mohammadi et al., 2004), cultural differences are important to consider since cultural norms relating to a range of ritualistic behaviors may differ (American Psychiatric Association Committee on Nomenclature and Statistics, 2000). Although cultural considerations exist for both IED and OCD, the nature of the associations between specific cultural factors and the two disorders appears to differ.

## 3. Pathological gambling (PG)

### 3.1. Phenomenology and epidemiology

PG has been hypothesized to represent both an OC-spectrum disorder and an addiction without a drug, and data exist to support each categorization (Hollander and Wong, 1995; Potenza et al., 2001a,b). While these categorizations are not mutually exclusive, they have important theoretical and clinical implications (Tamminga and Nestler, 2006). Repetitive, intrusive thoughts about gambling in PG share features with obsessions in OCD. Like OCD, PG is characterized by repetitive behaviors. In PG, gambling and gambling-related behaviors (e.g., handicapping, getting money to gamble) are performed repeatedly (Potenza et al., 2001a,b). As with OCD, the behaviors typically interfere significantly with major areas of functioning (American Psychiatric Association Committee on Nomenclature and Statistics, 2000). In contrast to the ego-dystonic behaviors related to OCD, gambling in PG is often initially ego-syntonic or hedonic in nature, although over time the pleasure derived from gambling may diminish. In this respect, the gambling in PG may be similar to drug use in drug dependence, and this and other phenomenological similarities have suggested that PG may represent a "behavioral addiction" (Holden, 2001; Petry, 2006; Potenza, 2006). A telescoping phenomenon has been reported for PG and in drug and alcohol dependence in which women on average initially engage in disorder-related behavior at a later age but progress more quickly ("telescope") than do men to problematic levels (Potenza et al., 2001a,b; Tavares et al., 2001). The ratio of men:women with PG (about 2:1) also resembles that in drug and alcohol dependence more than the ratio seen in OCD (about 1:1) (Potenza et al., 2001a,b; Petry, 2006; Potenza, 2006). The existing data on the clinical courses of PG and substance dependence also suggest similarities, with negligible rates in childhood, high rates in adolescence and young adulthood, and lower rates in older adults (Chambers and Potenza, 2003; Potenza, 2006). These patterns differ from those observed in OCD. For example, in OCD, onset during childhood is relatively common (American Psychiatric Association Committee on Nomenclature and Statistics, 2000). Many inclusionary diagnostic criteria for PG are more reflective of those for substance dependence, including aspects of tolerance, withdrawal, repeated unsuccessful attempts to cut back or quit, and interference in major areas of life functioning. Personality measures suggest that individuals with PG, like those with substance dependence, are impulsive and sensation-seeking (Blaszczynski et al., 1997; Potenza et al., 2003b) whereas those with OCD are more harm-avoidant (Hollander and Wong, 1995; Anholt et al., 2004). Thus, although there are phenomenological similarities between PG and OCD, those between PG and substance dependence appear more robust.

### 3.2. Co-occurring disorders

Studies of clinical samples indicate high rates of co-occurrence between PG and a broad range of internalizing and externalizing disorders, including both axis I and axis II conditions (Crockford and el-Guebaly, 1998; Potenza, 2007). Data from community samples also indicate high rates of co-occurring disorders. For example, data from the St. Louis Epidemiologic Catchment Area (ECA) study found

elevated odds ratios between problem/pathological gambling and major depression, anxiety disorders (phobias, somatization), drug use disorders (nicotine dependence and alcohol abuse/dependence), psychotic disorders, and antisocial personality disorder (Cunningham-Williams et al., 1998). A non-elevated odds ratio of 0.6 was observed between problem/pathological gambling and OCD (Cunningham-Williams et al., 1998). Other large community samples (e.g., the sample of male twins in the Vietnam Era Twin (VET) registry) have also shown elevated associations between PG and mood, anxiety, substance use, and antisocial personality disorders (Potenza et al., 2005). More recently, data from the NESARC indicated elevated odds ratios for PG in association with numerous axis I and axis II disorders including alcohol, nicotine and other drug dependence, mood disorders (including manic and depressive episodes), anxiety disorders (including panic, phobic and generalized anxiety), and personality disorders (including avoidant, dependent, obsessive–compulsive, paranoid, schizoid, histrionic, and antisocial) (Petry et al., 2005). In neither the NESARC nor the VET samples were diagnostic assessments of OCD obtained. Thus, existing community-based data suggest a stronger connection between PG and a broad range of other psychiatric disorders than is found between PG and OCD.

### 3.3. Family history and genetics

Twin studies indicate that PG has a high rate of heritability. A study of 3359 male twin pairs concluded that heredity explained from 35% to 54% of the liability for PG (Eisen et al., 1998; Shah et al., 2005). These findings are consistent with a smaller family history study in which estimates of PG in relatives of probands with PG were 9%, substantially higher than the 1% rate typically observed in the general population (Black et al., 2003). Consistent with the existing data on co-occurring disorders, family history studies do not indicate high rates of PG among family members of probands with OCD (Hollander et al., 1997; Bienvenu et al., 2000). Also consistent with patterns of co-occurring disorders seen in population-based samples (Cunningham-Williams et al., 1998; Petry et al., 2005), data from the VET registry indicate significant genetic and environmental contributions to PG and to its co-occurrence with alcohol dependence (Slutske et al., 2000) and antisocial behaviors (Slutske et al., 2001). In comparison, the overlap between PG and major depression is predominantly attributable to shared genetic factors (Potenza et al., 2005). Similar studies probing the relationship between PG and OCD have not been reported.

Candidate gene studies have suggested that multiple commonly occurring allelic variants contribute to PG (Ibanez et al., 2003; Shah et al., 2004). The Taq-A1 polymorphism of the gene encoding the D2 dopamine receptor has been associated with PG, attention deficit hyperactivity disorder, Tourette's syndrome, alcohol and drug abuse/dependence, antisocial behaviors, and poor inhibitory control (Blum et al., 1996; Comings, 1998; Ponce et al., 2003; Rodriguez-Jimenez et al., 2006). Other allelic variants including those in genes coding for the D1 dopamine receptor, monoamine oxidase A enzyme, and the 5HT transporter, among others, have been implicated in PG (Perez de Castro et al., 1997; Comings, 1998; Perez de Castro et al., 1999; Comings et al., 2001; Ibanez et al., 2003; Shah et al., 2004; Williams and Potenza, 2008). Although some of the same allelic variants (e.g., variants of the 5HT transporter gene) have been implicated in OCD and PG, the nature of the association has differed, with the long allele found in association with OCD and the short allele found in association with PG (Ibanez et al., 2003; Hemmings and Stein, 2006). Moreover, the findings in OCD have been inconsistent, with several studies implicating the allele and others not (Hemmings and Stein, 2006). Numerous limitations exist in the candidate gene studies performed to date in PG. For example, some studies have not included diagnostic assessments or considered differences in racial/ethnic compositions between groups. As a result, these studies should be regarded as preliminary, with more work needed to identify the specific genetic contributions to PG and how they compare and contrast with those underlying OCD.

### 3.4. Neurobiology: animal models and human studies

Although animal models of PG per se have not been established, frontostriatal circuitry has been implicated across species in tasks involving impulsive choice (Jentsch and Taylor, 1999; Schultz et al., 2000; Everitt and Robbins, 2005). This circuitry has also been implicated in human studies of PG (Potenza, 2001; Potenza, 2006; Williams and Potenza, 2008). Brain-imaging studies of individuals with PG have implicated vmPFC during gambling urges (Potenza et al., 2003b), cognitive control (Potenza et al., 2003a), and simulated gambling (Reuter et al., 2005). In non-PG subjects, this brain region is involved in cognitive processes relevant to gambling, including reward processing (Knutson et al., 2001; McClure et al., 2004) and risk-reward decision-making (Bechara et al., 1998, 1999; Bechara, 2003). Studies of performance on neurocognitive tasks targeting these processes have revealed differences between PG and control comparison subjects (Petry and Casarella, 1999; Petry, 2001; Cavedini et al., 2002a). Differences between PG and control subjects in decision-making task performance have been found (Cavedini et al., 2002a), and these differences are similar to those between OCD and control subjects (Cavedini et al., 2002b) and those between drug dependent and control subjects (Bechara, 2003). However, the brain activations underlying these between-subject-group differences on decision-making tasks have not been directly examined. Given that increased activation of frontostriatal circuitry has been repeatedly observed in OCD (Mataix-Cols and van den Heuvel, 2006) and diminished activation seen in PG (Reuter et al., 2005; Potenza, 2006), concurrent investigation of PG, OCD, drug dependent and control subjects on the neural correlates of cognitive processes relevant to these subject groups is needed.

Pharmacological challenge studies have implicated multiple neurotransmitter systems in PG, including 5HT, dopamine, norepinephrine opioid and other systems (Potenza, 2001; Potenza and Hollander, 2002; Chambers and Potenza, 2003). Many of these systems are implicated in other psychiatric disorders including OCD, in which data indicating involvement of 5HT and dopamine systems are well substantiated (Pauls et al., 2002). However, data suggest differences in the nature of the involvement of these systems in PG and OCD. Studies in OCD subjects of pro-serotonergic agents like *m*-CPP indicate that a substantial proportion (about 50%) report a transient worsening of symptoms following drug challenge (Pauls et al., 2002). In contrast, individuals with PG are more likely to report a euphoric or "high" response to pro-serotonergic agents (Potenza and Hollander, 2002). These findings not only complement brain-imaging findings in which similar paradigms suggest between-group differences of opposite valences in OCD and PG (Potenza et al., 2003b), but also suggest that specific components of impulsivity (e.g., those related to euphoria in relationship to disinhibition) may be linked to specific components of the 5HT systems.

### 3.5. Pharmacological and behavioral treatments and interventions

Over the past decade our understanding of safe and effective treatments for PG has advanced considerably (Grant and Potenza, 2004, 2007; Brewer et al., 2008). Both similarities and differences are evident with respect to pharmacological treatments for PG and OCD. First-line pharmacotherapy for OCD involves the use of SRIs, drugs that have been shown in multiple placebo-controlled, randomized clinical trials (RCTs) to be effective (Denys, 2006). The role for SRIs in the treatment of PG is less clear. While several RCTs have found SRIs like fluvoxamine and paroxetine to be superior to placebo in the treatment of PG (Hollander et al., 2000; Kim et al., 2002), others have

not found a statistically significant effect (Blanco et al., 2002; Grant et al., 2003). These findings suggest that there exist significant individual factors related to treatment outcome in groups of individuals with PG. Considering co-occurring disorders might be one method for guiding pharmacotherapies (Hollander et al., 2004; Potenza, 2007). For example, a recent study of escitalopram in the treatment of PG and co-occurring anxiety found concurrent reduction in anxiety and gambling symptoms during open-label treatment (Grant and Potenza, 2006b). In subjects receiving active drug during the double-blind discontinuation phase, clinical response was maintained; in contrast, placebo treatment was associated with symptom worsening (Grant and Potenza, 2006b). Emerging data suggest roles for glutamatergic therapies in the treatment of both OCD and PG (Denys, 2006; Grant, 2006). However, the results from these and most other pharmacotherapy trials of PG should be considered cautiously given such limitations as small sample sizes and short-term treatment durations. Particular caution is warranted with respect to open-label findings given high placebo response rates observed in PG studies (Grant and Potenza, 2004).

Results of other pharmacotherapy trials suggest differences between PG and OCD. For example, opioid antagonists like naltrexone and nalmefene have been found to be superior to placebo in the treatment of PG (Kim et al., 2000; Grant et al., 2006b). In contrast, the opioid antagonist naloxone has been associated with symptom exacerbation with OCD (Insel and Pickar, 1983; Keuler et al., 1996). Whereas mood stabilizers like lithium may be helpful in groups of subjects with PG (Hollander et al., 2005), their efficacy in OCD seems questionable (McDougle et al., 1991). Whereas anti-psychotic drugs that antagonize D2 dopamine receptors (e.g., haloperidol, risperidone and olanzapine) have shown efficacy as augmenting agents in OCD (Denys, 2006), existing data do not support a role for these drugs in the treatment of PG (Grant and Potenza, 2004).

Data suggest that behavioral therapies have important roles in the treatment of PG and OCD. However, the specific behavioral interventions differ. In PG, the 12-step program Gamblers Anonymous (GA) is arguably the most widely used intervention and existing data suggest that those who attend fare better than those who do not (Petry, 2005; Brewer et al., 2008). The extent to which this represents a true treatment effect or reflects selection bias (i.e., those motivated to stay in GA are also motivated not to gamble) warrants more investigation. GA, an intervention with limited economic burden, is modelled after Alcoholics Anonymous. No similarly organized 12-step program is established for or believed to be helpful for individuals with OCD. Behavioral therapies helpful for individuals with PG include motivational enhancement or interviewing and cognitive behavioral therapy (Sylvain et al., 1997; Hodgins et al., 2001; Petry et al., 2006; Grant and Potenza, 2007; Brewer et al., 2008). These approaches tend to be modelled after the ones with demonstrated efficacy in the treatment of drug addiction (Miller, 1995; Carroll et al., 1998) rather than the exposure/response prevention strategies that are effective for treating OCD (Hohagen et al., 1998; Neziroglu et al., 2006).

### 3.6. Cultural considerations

Both PG and OCD are present across cultures. Cultural differences relating to social acceptability and availability of legalized gambling might influence rates of PG (Shaffer et al., 1999). As with OCD, largely similar estimates of PG prevalence have been observed in studies around the world (Cunningham-Williams and Cottler, 2001; Abbott et al., 2004). Nonetheless, certain populations [e.g., southeast Asian immigrants (Petry, 2003)] have particularly high rates of gambling problems. The precise reasons for these findings require additional investigation. Environmental contributions that might differ across cultures and contribute to PG are likely to differ from those

contributing to OCD, but more research is needed to investigate this notion directly.

## 4. Conclusions, existing limitations and future directions

While ICDs resemble OCD in some domains, existing data suggest substantial differences between ICDs and OCD. Although progress has been made over the last decade in understanding ICDs and OCD, existing data are often limited and include methodological concerns that are sometimes severe and complicate interpretation and comparisons across subject groups. Methodological limitations include ascertainment bias affecting the samples evaluated, small study samples, error-prone methods of data-gathering (e.g., gathering family history from probands without confirmatory interviews of family members), differing methods of establishing diagnoses (e.g., structured versus unstructured interviews) and differing methods of examining biological characteristics (e.g., different methods of brain imaging). For many data domains (e.g., genetics, neurobiology and immune function), there exist little or no data for many of the ICDs and only limited data for OCD. The group of ICDs as a whole remains understudied and specific ICDs (e.g., pyromania and kleptomania) receive particularly little attention from the research and clinical communities. Other proposed ICDs (including compulsive buying or shopping, compulsive computer use or problematic internet use, compulsive sexual behavior, compulsive skin-picking/nail-biting) need further examination. For these ICDs, it is recommended that diagnostic criteria be derived for DSM-V from examinations of large samples of clinical cases or of subjects ascertained through random-sample community surveys (Koran et al., 2006; Abou-jaoude et al., 2006). ICDs, when present, often go unrecognized within clinical settings (Grant et al., 2005; Grant et al., 2007), and this under-recognition is associated with sub-optimal treatment outcomes in multiple domains (Potenza, 2007). Thus, increased efforts to identify ICDs are needed to enhance clinical care (Chamberlain et al., 2007).

Numerous gaps exist in our understanding of ICDs and their relationships with OCD and other psychiatric disorders. Additional research is needed to obtain evidence for clustering individual ICDs together or to support alternate categorizations (Lochner et al., 2005). From a broader perspective, it is important to examine the relationships between non-ICD psychiatric disorders and individual ICDs or empirically derived groups thereof. These investigations will have not only theoretical implications for grouping the disorders, but also direct clinical relevance given the high rates of co-occurring disorders observed in individuals with ICDs (Potenza, 2007). As ICDs often have elements consistent with relationships with several psychiatric disorders [e.g., addictions and OCD (Grant et al., 2007)], investigations of dimensional as well as categorical measures of psychiatric symptomatology are needed (Saxena et al., 2005; Muthen, 2006). Within each ICD, identification of individual characteristics that differentiate subgroups of individuals with unique treatment needs is important. Identification of relevant endophenotypes that can facilitate prevention and treatment advances is needed and should include an understanding of specific environmental, genetic and interactive influences (Gottesman and Gould, 2003; Kreek et al., 2005). The potential clinical utilities of these specific individual differences or endophenotypes in targeting behavioral and pharmacological interventions and for identifying high- versus low-risk individuals require direct examination. Among the most salient needs is an improved understanding of the pathophysiologies of ICDs. Additional large-scale molecular genetic and brain-imaging studies are needed to better understand the biological underpinnings of the disorders and to translate this information into clinical advances in prevention and treatment.

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