

Intermittent Explosive Disorder as a Disorder of Impulsive Aggression for DSM-5

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A disorder of impulsive aggression has been included in DSM since the first edition. In DSM-III, this disorder was codified as intermittent explosive disorder, and it was thought to be rare. However, the diagnostic criteria for the disorder were poorly operationalized, and empirical research was limited until research criteria were developed a decade ago. Subsequently, renewed interest in disorders of impulsive aggression led to a recent series of community-based studies that have documented intermittent explosive disorder to be as common as many other psychiatric disorders. Other recent research indicates

that compared with DSM-IV criteria for intermittent explosive disorder, research criteria for the disorder better identify individuals with elevated levels of aggression, impulsivity, familial risk of aggression, and abnormalities in neurobiological markers of aggression. In addition, other data strongly suggest important delimitation from other disorders previously thought to obscure the diagnostic uniqueness of intermittent explosive disorder. Overall, these data suggest that the diagnostic validity for the integrated research criteria is substantial and is now sufficient for recognition and inclusion in DSM-5.

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Human aggression constitutes a multidetermined act that results in physical or verbal injury to self, others, or objects. It appears in several forms and may be defensive, premeditated (e.g., predatory), or impulsive (nonpremeditated) in nature. While defensive aggression is in the normal range of human behavior, premeditated and impulsive aggression are viewed as pathological. The tendency to behave aggressively on more than an isolated basis represents a behavioral trait that begins early in life and continues through adulthood. Impulsive and premeditated aggression are both associated with significant physical and psychosocial harm to the aggressive individual, to victims of the aggression, and to society. However, a converging pattern of data consistently links impulsive, but not premeditated, aggression to biological (1), environmental (2), pharmacological (3, 4), and psychological (5) treatment response factors. Epidemiological data from a variety of sources suggest that “recurrent, problematic, impulsive aggression” (defined as intermittent explosive disorder) affects some 5%–7% of the U.S. population (6) and no less than 6% of those presenting for treatment at outpatient psychiatry clinics (7)—a low number given that most individuals with intermittent explosive disorder do not seek treatment (6, 7). Accordingly, intermittent explosive disorder appears to represent a common behavioral disorder amenable to treatment by specific pharmacological or psychological treatment interventions.

History of Intermittent Explosive Disorder

While the term “intermittent explosive disorder” did not appear in DSM until publication of the third edition in 1980, a “disorder of impulsive aggression” has been included since the first edition in 1952. In DSM-I, this disorder was called “passive-aggressive personality, aggressive type.” It was characterized as “persistent reaction to frustration with irritability, temper tantrums, and destructive behavior.” This disorder became “explosive personality” in DSM-II in 1968. Individuals with explosive personality were “aggressive individuals” who displayed “intermittently violent behavior” and were “generally excitable, aggressive, and overresponsive to environmental pressures” with “gross outbursts of rage or of verbal or physical aggressiveness different from their usual behavior.” In DSM-III, “explosive personality” was codified as “intermittent explosive disorder” for the first time and assigned axis I clinical disorder status. Criteria for the disorder, however, were poorly operationalized and problematic. For example, individuals who were generally aggressive or impulsive in between the ill-defined “aggressive episodes” could not receive a diagnosis of intermittent explosive disorder. However, since individuals with recurrent, problematic, impulsive aggression are also generally impulsive and aggressive between their more severe outbursts, this exclusion ruled out the

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FIGURE 1. DSM-IV and Research Criteria for Intermittent Explosive Disorder

DSM-IV Criteria	
A.	Several discrete episodes of failure to resist aggressive impulses that result in serious assaultive acts or destruction of property.
B.	The degree of aggressiveness expressed during the episodes is grossly out of proportion to any precipitating psychosocial stressors.
C.	The aggressive episodes are not better accounted for by another mental disorder (e.g., antisocial personality disorder, borderline personality disorder, a psychotic disorder, a manic episode, conduct disorder, or attention deficit hyperactivity disorder) and are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., head trauma, Alzheimer's disease).
Research Criteria	
A.	Recurrent incidents of aggression manifest as either: A1. verbal or physical aggression towards other people, animals, or property occurring twice weekly on average for one month OR A2. three episodes involving physical assault against other people or destruction of property over a one year period.
B.	The degree of aggressiveness expressed is grossly out of proportion to the provocation or any precipitating psychosocial stressors.
C.	The aggressive behavior is not premeditated (i.e., is impulsive) and is not committed to achieve some tangible objective (e.g., money, power, intimidation, etc.).
D.	The aggressive behavior causes either marked distress in the individual or impairment in occupational or interpersonal functioning.
E.	The aggressive behavior is not better accounted for by another mental disorder (e.g., major depressive disorder, a manic episode, a psychotic disorder), a general medical condition (e.g., head trauma, Alzheimer's disease), or the direct physiological effects of a substance (e.g., a drug of abuse, a medication).

vast majority (about 80%) of individuals who can now be diagnosed as having intermittent explosive disorder (8). While revisions to the criteria in 1994 for DSM-IV allowed for more empirical work to be done, the development of research criteria (9) was necessary for empirical research on intermittent explosive disorder to begin in earnest.

Research Criteria for Intermittent Explosive Disorder

Research criteria for intermittent explosive disorder, developed by Coccaro and colleagues (9, 10), make five important revisions to the DSM-IV criteria (Figure 1). First, the research criteria operationalize the scope and frequency/time-frame characteristics of aggressive behavior required for diagnosis so that intermittent explosive disorder can be diagnosed in the presence of high-frequency/low-intensity (criterion A1) or low-frequency/high-intensity (criterion A2) aggressive outbursts. The A1 threshold was set at an average of two outbursts a week for at least 1 month because this level of low-intensity aggression responds well to pharmacological (11) and cognitive-behavioral (5) interventions and does not differ in psychometric

(10) or analogue laboratory (12) assessments of aggression from low-frequency/high-intensity aggressive behavior. The A2 threshold was set at three severe outbursts a year because this level of high-intensity aggression distinguishes individuals who are significantly more aggressive, on a variety of parameters, compared with those with a lower frequency of severe aggressive outbursts (Table 1).

Second, the research criteria require that the aggressive behavior be impulsive in nature, an important distinction since empirical data clearly separate impulsive from premeditated aggression (1–4). Third, the research criteria require that subjective distress or social or occupational dysfunction be linked to the aggressive behavior. Fourth, the research criteria allow subjects with antisocial or borderline personality disorder or with disruptive behavior disorders (conduct disorder, oppositional defiant disorder, or attention deficit hyperactivity disorder [ADHD]) to be diagnosed with intermittent explosive disorder if they otherwise meet the research criteria. While individuals with antisocial personality disorder, borderline personality disorder, or disruptive behavior disorders are often aggressive, only those who also meet criteria for intermittent explosive disorder are as aggressive as those who have intermittent explosive disorder alone. Fifth, the research criteria disallow the diagnosis for subjects with a current history of major depression, mania, or psychosis.

Construct Validity of Intermittent Explosive Disorder

The construct validity of a psychiatric disorder can be assessed through examination of clinical description, taxonomic analysis, epidemiology, stability over time, delimitation from other disorders, family study, and neurobiological/treatment study correlates.

Clinical Description: Phenomenology

Aggressive outbursts in intermittent explosive disorder have a rapid onset (13) and typically have little or no prodromal period (8, 14). Episodes typically last less than 30 minutes (13) and involve verbal assault, destructive and nondestructive property assault, or injurious or noninjurious physical assault (13, 14). Aggressive outbursts most commonly occur in response to a minor provocation by a close intimate or associate (8, 13), and subjects with intermittent explosive disorder often have less severe episodes of verbal and nondestructive property assault in between the more severe assaultive/destructive episodes (10, 14). Episodes are associated with substantial distress, impairment in social functioning, occupational difficulty, and legal or financial problems (13, 14). In the largest community sample studied in the United States (6), subjects meeting a "narrow" definition of DSM-IV intermittent explosive disorder (i.e., three high-severity episodes in the current year—comparable to the research criteria) were found to engage in direct interpersonal aggression

TABLE 1. Distinctions Between Narrow and Broad-Only Definitions of Intermittent Explosive Disorder by DSM-IV Criteria^a

Measure	Narrow Criteria		Broad-Only Criteria		t	df	Effect Size (d)	p
	Mean	SD	Mean	SD				
Number of years with aggressive outbursts ^b	11.8	12.9	6.2	6.4	5.30	623	0.50	<0.001
Highest number of aggressive outbursts in any one year ^b	27.8	88.2	1.6	1.3	3.78	623	0.40	<0.001
Number of aggressive outbursts in past year ^c	11.8	21.2	1.3	0.7	3.46	277	0.60	<0.001
Number of weeks with aggressive outbursts in past year ^c	19.6	42.5	1.3	0.7	3.01	277	0.52	<0.003
Number of aggressive events resulting in medical attention (lifetime) per individual ^c	2.3	11.0	0.4	1.5	2.28	277	0.22	<0.030
Value (in dollars) in property damage by individual (lifetime) ^b	1,601	2,904	447	1,718	4.77	623	0.44	<0.001
Severe role impairment score due to aggressive outbursts ^c	40.4	54.6	19.6	45.5	2.49	277	0.39	<0.015

^a Data from Kessler et al. (6).^b Narrow criteria, N=463; broad-only criteria, N=162.^c Narrow criteria, N=230; broad-only criteria, N=49.

(67.8%), to threaten interpersonal aggression (20.9%), and to engage in aggression against objects (11.4%). Subjects meeting only a “broad” definition of the disorder (i.e., at least three high-severity aggressive outbursts over the lifetime but not three in any 1 year) were found to be far less aggressive and far less impaired as a result of aggression than those meeting the narrow criteria. Table 1 summarizes the differences in critical aggression and impairment measures between those meeting narrow and those meeting broad-only criteria. All differences were statistically significant, and the effect sizes, on average, were nearly medium sized (mean=0.41, SD=0.11). Individuals who meet the narrow but not the broad-only definition would meet research criteria for the disorder. Where possible, the narrow as well as the broad (which includes those meeting the narrow) definition for DSM-IV intermittent explosive disorder is used in this article.

Taxonomic Characteristics: Categorical or Dimensional?

Special analytical methods have been developed to determine whether constructs such as behavioral disorders are best viewed as categorical (taxonic) or dimensional in nature (15). If taxonic, a diagnostic group is better conceived as a distinct entity. If dimensional, the diagnostic group represents the pathological end of a continuum of normal behavior. Some behavior disorders have been shown by taxometric analyses to be dimensional (e.g., posttraumatic stress disorder [16], antisocial personality disorder [17], borderline personality disorder [18, 19]), while others have been shown to be taxonic (e.g., schizotypal personality disorder [19, 20]). Despite the fact that impulsive aggression is dimensional in nature, a recent taxometric analysis (21) found that intermittent explosive disorder is taxonic and not dimensional in nature. The investigators examined 28 items related to intermittent explosive disorder that were completed during the Collaborative Psychiatric Epidemiological Survey (N=20,013)

(22). The items were then combined into seven composite indicators and mapped onto both DSM-IV criteria and the research criteria. Taxometric analysis (23) yielded a profile consistent with a taxonic rather than a dimensional structure for intermittent explosive disorder. Taxon group membership was also associated with treatment seeking, family history of aggressive outbursts, lower age at onset of these outbursts, and male gender, factors that characterize individuals with intermittent explosive disorder (see below).

Epidemiology

Prevalence. Intermittent explosive disorder was thought to be rare until recently, when a number of community sampling studies were published beginning in the mid-2000s. Lifetime and past-year prevalence data for DSM-IV intermittent explosive disorder from 12 community sampling studies (6, 24–34) are summarized in Table 2. In all studies, DSM-IV intermittent explosive disorder was reported by the broad definition (three or more aggressive outbursts, lifetime), which also encompasses those meeting the narrow definition. In four studies, intermittent explosive disorder was also reported by the narrow definition. The weighted prevalence of lifetime DSM-IV intermittent explosive disorder in the United States is about 6.9% (~21 million people) for all intermittent explosive disorder and 5.4% for the narrow definition (~16 million people). The weighted lifetime prevalence for DSM-IV intermittent explosive disorder in the nine non-U.S. countries surveyed to date is 3.0%, which accounts for about 16 million lifetime cases in these countries. Weighted lifetime prevalence for the narrow definition is about 1.4% in the two countries that report such data. The relatively lower prevalence of the disorder in some regions (Asia, the Middle East) and some countries (Romania, Nigeria) compared with the United States is notable and suggests either that information about aggressive behaviors is not elicited on questioning or that such behaviors are less likely to be present, as a result of cultural factors. Overall, the lifetime

TABLE 2. Summary of Prevalences of DSM-IV Intermittent Explosive Disorder in Community Studies

Region and Study Authors (Reference)	Country	N	Prevalence (%)			
			All Cases		Narrow Criteria ^a	
			Lifetime	Past Year	Lifetime	Past Year
North America						
Coccaro et al. (24)	United States	253	4.0	1.6	5.1	2.0 ^b
Kessler et al. (6)	United States	9,282	7.3	3.9	5.4	2.7
Ortega et al. (26)	United States	2,554	5.8	4.1	NR	NR
Weighted average	United States	12,089	6.9	3.9	5.4	2.7
South America						
Posada-Villa et al. (27)	Columbia	4,426	4.7	2.9	NR	NR
Europe						
Bromet et al. (25)	Ukraine	4,725	4.2	2.8	NR	NR
Florescu et al. (31)	Romania	2,537	1.3	NR	NR	NR
Asia						
Huang et al. (28)	China	5,201	1.9	1.2	NR	NR
Yoshimasu and Kawakami (34)	Japan	4,134	2.1	0.7	1.2	0.6
Africa						
Gureje et al. (29)	Nigeria	6,752	0.2	0.2	NR	NR
Fincham et al. (32)	S. Africa	4,351	9.5	1.8	2.0	NR
Middle East						
Karam et al. (30)	Lebanon	2,857	1.7	0.8	NR	NR
Alhasnawi et al. (33)	Iraq	4,332	1.7	1.5	NR	NR
Weighted average	Non-U.S. countries	39,315	3.0	1.4	1.6	0.6

^a NR=not reported.^b Past month only.

and past-year prevalences of intermittent explosive disorder are far greater than previously thought.

Sociodemographic correlates. In clinical reports, DSM-IV intermittent explosive disorder appears to be more frequent in males than in females, by a 2:1 ratio (9, 13, 14). In community survey samples, however, the odds ratio for males compared with females was significant in only three of 12 studies, with a range of 1.4 to 2.3 (6, 26, 34). Other sociodemographic variables (e.g., age, race, education, marital status, occupational status, family income) similarly display varying but modest correlations with intermittent explosive disorder. For age, intermittent explosive disorder is more prevalent among younger (<35–40 years) compared with older (>50 years) individuals (6, 25, 34). In U.S. studies, the disorder is nearly twice as prevalent among individuals in the “other” race category (those who are not white, black, or Hispanic) (6). For education, only two community studies report an effect of education on intermittent explosive disorder in which having ≤12 years of education is associated with a greater odds ratio for the disorder compared with having more years of education. For the remaining sociodemographic variables, a clear relationship was reported between intermittent explosive disorder and marital status, employment status, or household income status in only one community study each.

Stability Over Time: Onset Age and Duration of Condition

DSM-IV intermittent explosive disorder appears as early as prepubertal childhood and peaks in mid-adolescence,

with a mean (or median) onset age, in seven separate studies, ranging from about 13 to 21 years (6, 24, 25, 27, 28, 33, 34). The average duration of symptomatic intermittent explosive disorder by DSM-IV or research criteria ranges from nearly 12 years (6) to 20 years (13) to nearly the whole lifetime (24). While no follow-up studies of DSM-IV intermittent explosive disorder have been conducted, available data suggest that onset of the disorder precedes onset of other comorbid disorders (6, 7) and that intermittent explosive disorder is persistent and follows a chronic course of at least 12 years. If so, it is unlikely that intermittent explosive disorder transforms into another disorder. More likely, it promotes the development of other disorders by leading to divorce, financial difficulties, and stressful life experiences that in turn promote the onset of other disorders later on in adulthood (6).

Delimitation From Other Psychiatric Disorders

Depressive mood, anxiety, and substance use disorders. In clinical reports, intermittent explosive disorder (by DSM-IV or research criteria) co-occurs with a variety of other axis I disorders, such as depressive (unipolar) mood, anxiety, and substance use disorders (7, 9). Community sampling studies report odds ratios for co-occurrence of intermittent explosive disorder with other axis I disorders (6, 25, 26, 34) that suggest that depressive and anxiety disorders are at least four times more prevalent and that substance use disorders are at least three times more prevalent in individuals with DSM-IV intermittent explosive disorder. Where data are available for onset age, the dis-

order begins at an earlier age than do these co-occurring conditions (6, 34). A large clinical study (7) also reported a significantly earlier onset age for DSM-IV intermittent explosive disorder than for depressive mood disorders, non-phobic anxiety disorders, and substance use disorders in subjects with both intermittent explosive disorder and the co-occurring disorder. In addition, some disorders (e.g., mood disorders, substance use disorders during intoxication and/or withdrawal) may themselves be associated with aggressive outbursts. Accordingly, intermittent explosive disorder should be diagnosed only when a sufficient number of aggressive outbursts occur to meet diagnostic criteria while the co-occurring disorder is not active.

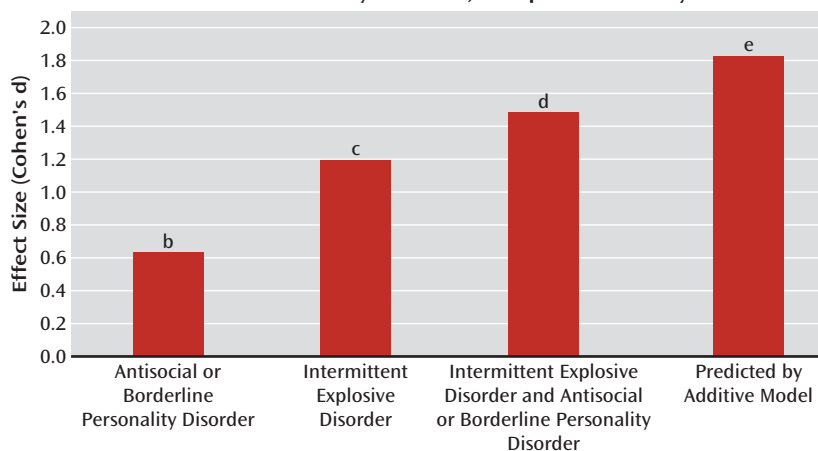
Bipolar disorder. A relationship between DSM-IV intermittent explosive disorder and bipolar disorder has been suggested by several in the field (13). Co-occurrence of the two disorders has been reported at nearly 60% in at least one clinical study, and aggressive episodes in some subjects with intermittent explosive disorder appear to resemble “micromanic episodes,” with manic-like affective symptoms (e.g., irritability, increased energy, and racing thoughts) occurring prior to and during aggressive episodes in 62%–99% of subjects with DSM-IV intermittent explosive disorder (13). In nearly all other published studies, the current co-occurrence of bipolar disorder is treated as exclusionary for the diagnosis of intermittent explosive disorder. The lifetime co-occurrence rate of DSM-IV intermittent explosive disorder and bipolar disorder is not zero, however. In at least two published clinical studies where such data are available, the lifetime co-occurrence of these two disorders was reported to be about 10% (6, 7). In the one study reporting data on onset age, the mean age at onset of DSM-IV intermittent explosive disorder preceded that for bipolar disorder by about 5 years (7). While this suggests delimitation of the two disorders, it may be that the presence of intermittent explosive disorder is a harbinger of the bipolar disorder to come. In the National Comorbidity Survey Replication study (6), DSM-IV intermittent explosive disorder diagnoses were not made when the course of the disorder fully overlapped with the course of bipolar I or II disorder (i.e., intermittent explosive disorder was ruled out by co-occurring bipolar disorder in 2.3% and 3.6% of cases by broad and narrow criteria, respectively). For the remainder of the cases, the rates of co-occurrence of bipolar disorder were 14.2% and 15.6% by broad and narrow criteria, respectively, with odds ratios in the same range as those reported for unipolar depressive, anxiety, and substance use disorders (odds ratios of 4.4 and 4.6 by broad and narrow criteria, respectively).

Other impulse control disorders. In a clinical report, McElroy et al. (13) reported that 44% of patients with DSM-IV intermittent explosive disorder had a history of other impulse control disorders, with co-occurrence rates for specific disorders ranging from 0% to 19%. Data from the largest clinical survey study of DSM-IV intermittent explosive

disorder (7) indicate a co-occurrence rate of 7.3%, which is not significantly greater than the rate in subjects without intermittent explosive disorder (3.9%; odds ratio=2.0, n.s.). As with bipolar disorder, the mean age at onset of intermittent explosive disorder was earlier than that for other impulse control disorders (by 10 years), suggesting that intermittent explosive disorder does not transform into another impulse control disorder. In a family history study of intermittent explosive disorder (using research criteria), familial risk of impulse control disorders in relatives of probands did not differ from that of relatives of controls, suggesting that impulse control disorders do not aggregate in families of intermittent explosive disorder probands, as would be expected if these disorders were meaningfully related. Furthermore, lifetime co-occurrence of intermittent explosive disorder with other impulse control disorders in the relatives of all probands in the study was less than 1%, which also suggests little, if any, link between intermittent explosive disorder and other impulse control disorders.

Axis II disorders. Axis II disorders have not been closely examined in community studies of intermittent explosive disorder. However, in two samples (in Philadelphia and Chicago) of psychiatric subjects with or without intermittent explosive disorder (using research criteria), our group found that only patients with comorbid antisocial and borderline personality disorders are more prevalent among subjects with intermittent explosive disorder than among those without. Odds ratios for antisocial (10.5) and borderline personality disorders (8.0) were statistically significant ($p<0.001$) and were similar across the two samples (E.F. Coccaro et al., unpublished 2012 data). This degree of co-occurrence may be due to higher levels of aggressive behavior in individuals with antisocial and/or borderline personality disorder. However, data from our subjects ($N=1,300$ combined) show that while individuals who have only antisocial and/or borderline personality disorder have higher Life History of Aggression scores than psychiatric comparison subjects (patients with axis I or II disorders who have neither intermittent explosive disorder nor antisocial or borderline personality disorder), Life History of Aggression scores among subjects who have only intermittent explosive disorder are twice as high (antisocial or borderline personality disorder compared with psychiatric comparison subjects, effect size=0.58 standard deviations; intermittent explosive disorder compared with psychiatric comparison subjects, effect size=1.15 standard deviations) (Figure 2). Thus, having antisocial or borderline personality disorder accounts for only half of the magnitude of aggression seen in subjects who have only intermittent explosive disorder. The effect size for subjects with both intermittent explosive disorder and antisocial or borderline personality disorder was 1.43 standard deviations, significantly less ($p<0.05$) than that predicted by the addition of the separate effects of intermittent explosive

FIGURE 2. Effect Sizes of Life History of Aggression Scores of Subjects With Intermittent Explosive Disorder (Research Criteria) With or Without Antisocial or Borderline Personality Disorder, Compared With Psychiatric Comparison Subjects^a



^a Psychiatric comparison subjects had axis I or II disorders other than intermittent explosive disorder, antisocial personality disorder, and borderline personality disorder.

^b $p < 0.05$ compared with psychiatric comparison subjects.

^c $p < 0.05$ compared with psychiatric comparison subjects and compared with subjects with antisocial or borderline personality disorder.

^d $p < 0.05$ compared with subjects with antisocial or borderline personality disorder and compared with subjects with intermittent explosive disorder.

^e $p < 0.05$ compared with subjects with intermittent explosive disorder and antisocial or borderline personality disorder.

disorder and antisocial or borderline personality disorder on aggression scores (1.73 standard deviations). Accordingly, the combined effect of intermittent explosive disorder and antisocial or borderline personality disorder on aggression scores is not greater than would be expected by adding the level of aggression attributable to antisocial or borderline personality disorder to the level of aggression attributable to intermittent explosive disorder. Multiple regression analysis of these data sets also reveals that the shared variance between intermittent explosive disorder and antisocial or borderline personality disorder is rather small at less than 10% ($R^2=0.096$), with antisocial personality disorder uniquely accounting for only 2.9% and borderline personality disorder for 4.0% of this variance with intermittent explosive disorder. Addition of composite aggression scores (assessment of life history of aggression and aggressive temperament) to the regression model reduced the relationship with antisocial or borderline personality disorder to statistically nonsignificant levels ($<0.3\%$ of the variance for each), suggesting that only aggressive, rather than nonaggressive, features of antisocial or borderline personality disorder have any relevance for the co-occurrence of these disorders. Also notable is the observation that rates of co-occurrence of intermittent explosive disorder (using research criteria) and antisocial or borderline personality disorder depend on the setting of ascertainment; the rate of antisocial or borderline personality disorder in subjects with intermittent explosive disorder is much smaller in community samples (25% [24]) than in clinical research samples (85% [E.F. Coccaro et al., unpublished 2012 data]). Further support for the distinction of intermittent explosive disorder from antisocial

and borderline personality disorders comes from taxonic analyses demonstrating that the latent structure of intermittent explosive disorder is categorical (21), while those of antisocial (35) and borderline personality disorders (18) are dimensional.

Disruptive behavior disorders in childhood. A critical issue for the field of psychiatry is how best to describe impulsive aggression in children or adolescents. Often these individuals are thought to have bipolar disorder, although many question this view. Additionally, the nature of the relationship between intermittent explosive disorder and disruptive behavior disorders is important because both sets of disorders begin in childhood or adolescence, and DSM-IV criteria suggest that intermittent explosive disorder should not be diagnosed in the presence of disruptive behavior disorders (note that DSM-IV actually states that the diagnosis of intermittent explosive disorder should not be given when other disorders “better explain” the clinical presentation). Examination of the National Comorbidity Survey Replication study data reveals a significant association between DSM-IV intermittent explosive disorder and disruptive behavior disorders. Lifetime co-occurrence rates of intermittent explosive disorder (narrowly defined) with disruptive behavior disorders were as follows: with conduct disorder, 19.3% (odds ratio=6.4, $p < 0.001$); with oppositional defiant disorder, 21.6% (odds ratio=6.5, $p < 0.001$); with ADHD, 17.2% (odds ratio=6.1, $p < 0.001$); and with all disruptive behavior disorders, 37.9% (odds ratio=7.3, $p < 0.001$). The rates of co-occurrence for the specific disruptive behavior disorders were lower and not statistically significant when more than one disrupt-

tive disorder was present (e.g., conduct disorder and oppositional defiant disorder; conduct disorder and ADHD; oppositional defiant disorder and ADHD). The co-occurrence rate of intermittent explosive disorder with conduct disorder in the absence of oppositional defiant disorder was 11.0% (odds ratio=5.8), and in the absence of ADHD, 16.3% (odds ratio=6.6). The co-occurrence rate of intermittent explosive disorder with oppositional defiant disorder in the absence of conduct disorder was 13.5% (odds ratio=6.1), and in the absence of or ADHD, 16.3% (odds ratio=6.8). The co-occurrence rate of intermittent explosive disorder with ADHD in the absence of conduct disorder was 14.1% (odds ratio=6.4), and in the absence of oppositional defiant disorder, 11.6% (odds ratio=6.4). When considering onset age and recency of disorder, the time frame of intermittent explosive disorder overlaps with that of disruptive behavior disorders in only about a third of cases of a history of both disorders (11.9% compared with 37.9%). Thus, only about 12% of those with DSM-IV intermittent explosive disorder would be excluded if the disorder cannot be diagnosed in the current presence of any disruptive behavior disorder.

This high co-occurrence between intermittent explosive disorder and disruptive behavior disorders may be expected since some form of aggression (or impulsivity) is part of the DSM-IV criteria for each disruptive behavior disorder. Examples of predatory or premeditated aggression (e.g., robbery, extortion, sexual abuse, physical cruelty) are described in the criteria for conduct disorder. Examples of impulsive aggression are described in the criteria for oppositional defiant disorder (e.g., arguing, temper tantrums). Impulsivity (e.g., blurts out answers, interrupts others), but not aggression, is a diagnostic feature of ADHD, and impulsive behavior typically correlates with aggressive behavior. Despite these relationships, multiple regression analysis of the National Comorbidity Survey Replication study data reveals that shared variance between DSM-IV intermittent explosive disorder (narrowly defined) and history of the three disruptive behavior disorders is less than 5% ($R^2=0.046$), with unique variance accounting for intermittent explosive disorder at less than 1% for each disruptive behavior disorder. Accordingly, the relationships among these disorders may not be as strong, or as interdependent, as they might appear in the co-occurrence data. Moreover, when we examined the effect of a lifetime history of disruptive behavior disorder on intermittent explosive disorder (using research criteria) in our own clinical research data sets, history of a disruptive behavior disorder does not account for the levels of aggression seen in intermittent explosive disorder (Figure 3). That is, the magnitude of the effect of a history of a disruptive behavior disorder on aggression scores (0.71 standard deviations; i.e., Life History of Aggression scores for psychiatric comparison subjects subtracted from scores for those with a disruptive behavior disorder alone) is less than the effect size for intermittent explosive disorder

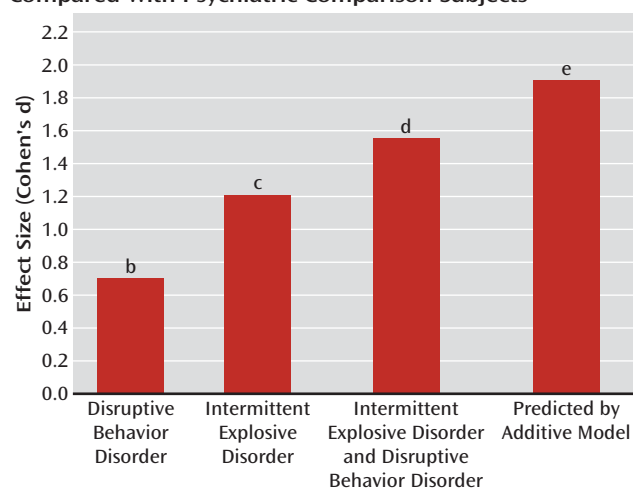
alone on aggression scores (1.22 standard deviations, $p<0.05$). While the corresponding effect size for disruptive behavior disorder history *and* intermittent explosive disorder on aggression scores (1.57 standard deviations) was significantly ($p<0.05$) greater than that of intermittent explosive disorder, it was less than that predicted by combining the effect sizes of aggression score attributable to a history of a disruptive behavior disorder with that attributable to intermittent explosive disorder (1.57 standard deviations compared with 1.92 standard deviations, $p<0.05$). Accordingly, the presence of a disruptive behavior disorder history alone falls short of explaining the greater degree of aggression seen in intermittent explosive disorder with a history of a disruptive behavior disorder.

Finally, when life history of aggression is accounted for, current severity of oppositional defiant disorder or ADHD symptoms (data were not available for current conduct disorder symptoms) was found to track with history of oppositional defiant disorder or ADHD, but not intermittent explosive disorder. In this regard, individuals with intermittent explosive disorder (using research criteria) are similar to psychiatric comparison subjects, while individuals with intermittent explosive disorder and a history of a disruptive behavior disorder are similar to those with a history of a disruptive behavior disorder alone. The difference between the two groups is substantial (effect size=1.0 standard deviation) and indicates that subjects with intermittent explosive disorder (without a history of a disruptive behavior disorder) do not display the level of oppositional defiant disorder or ADHD psychopathology that would be expected if these were the same disorders by different names. Accordingly, individuals with intermittent explosive disorder and a history of a disruptive behavior disorder display the same level of oppositional defiant disorder or ADHD psychopathology as those with oppositional defiant disorder or ADHD alone because of the co-occurrence of these disruptive behavior disorders. Separation of intermittent explosive disorder from the disruptive behavior disorders is also suggested by taxometric analyses reporting that the latent structure of conduct disorder (36), ADHD (37), and oppositional defiant disorder (E.F. Coccaro et al., unpublished 2012 data) are dimensional while that of intermittent explosive disorder (21) is categorical. While all these data suggest the independence of intermittent explosive disorder from the disruptive behavior disorders, confirmation of these observations must await the prospective, longitudinal study of children and adolescents in which data relevant to the criteria for intermittent explosive disorder and disruptive behavior disorders are simultaneously collected.

Family Study

Existing family history data suggest that intermittent explosive disorder is familial. In an uncontrolled study, McElroy et al. (13) noted that 32% of first-degree relatives of intermittent explosive disorder (using DSM-IV criteria) probands had the disorder. A more recent controlled,

FIGURE 3. Effect Sizes of Life History of Aggression Scores of Subjects With Intermittent Explosive Disorder (Research Criteria) With or Without Disruptive Behavior Disorders, Compared With Psychiatric Comparison Subjects^a



^a Psychiatric comparison subjects had axis I or II disorders but no history of intermittent explosive disorder or disruptive behavior disorders.

^b $p < 0.05$ compared with psychiatric comparison subjects.

^c $p < 0.05$ compared with psychiatric comparison subjects and compared with subjects with a history of a disruptive behavior disorder.

^d $p < 0.05$ compared with subjects with a history of a disruptive behavior disorder and compared with subjects with intermittent explosive disorder.

^e $p < 0.05$ compared with subjects with intermittent explosive disorder and a history of a disruptive behavior disorder.

blinded study reported an increase in the familiarity of intermittent explosive disorder (using research criteria) in probands with the disorder compared with probands without it (morbid risk, 0.35 compared with 0.10, $p < 0.001$) (38). The increase in morbid risk for familial intermittent explosive disorder in relatives of probands was also present when antisocial and borderline personality disorders were excluded from analysis. Elevation in the morbid risk for intermittent explosive disorder was not due to comorbid conditions among the probands (e.g., history of suicide attempt, major depression, alcoholism, a drug use disorder) and was not due to increases in morbid risk of psychiatric disorders other than intermittent explosive disorder in relatives. Accordingly, intermittent explosive disorder appears to demonstrate a clear familial transmission “signal.” Since twin studies have shown that impulsive aggression is under a substantial degree of genetic influence (39), much of this familial signal is likely due to genetic influence.

Psychological Correlates

Intermittent explosive disorder (using research criteria) is associated with elevated scores on a variety of psychometric assessments beyond the typical measures of physical or verbal aggression and of impulsivity. Individuals with the disorder have elevated levels of relational aggression (40), suggesting that aggressive impulses extend to behavior aimed at damaging interpersonal relationships (41). Compared with healthy and psychiatric comparison subjects, individuals with intermittent explosive disorder (research criteria) also demonstrate 1) greater hostile attribution bias and greater negative emotional responding to socially ambiguous stimuli (42), suggesting a psychological mechanism that triggers impulsive aggressive outbursts; 2) greater affective lability (12) and affective intensity; and 3) a greater degree of immature defense mechanisms, including acting out, dissociation, projection, and rationalization (E.F. Coccaro et al., unpublished 2012 data).

Psychosocial Antecedents

While a history of trauma in childhood has long been thought to be associated with the development of aggression in childhood and later on in adolescence (43), few data have been published on the association of trauma and intermittent explosive disorder. One community survey study (32) reported a significant association between history of trauma and intermittent explosive disorder in a South African sample. In that study, a history of trauma was more common among subjects with narrowly defined intermittent explosive disorder, especially those with trauma related to being a victim of crime, trauma to a close other, or a history of multiple traumas (i.e., six or more traumatic life events). In data collected at our research site, we found significantly higher scores on the Childhood Trauma Questionnaire (44) in subjects with intermittent explosive disorder (using research criteria) compared with axis I and II comparison subjects, who in turn had higher scores than healthy comparison subjects (26). Childhood Trauma Questionnaire scores are also directly correlated with hostile attribution bias scores, which are significantly greater in individuals with intermittent explosive disorder (research criteria) (42).

Neurobiological Studies

While neurobiological studies clearly show a biobehavioral relationship between aggression and selected brain chemicals, such as serotonin, studies of intermittent explosive disorder have only been conducted over the past few years. Subjects with intermittent explosive disorder (using research criteria) have been reported to have altered serotonin function compared with subjects without the disorder or healthy comparison subjects (45–51); they have lower numbers of platelet 5-HT transporters (via [³H] paroxetine binding) (46) and a lower magnitude of the prolactin response to *d,l*-fenfluramine (49) and to *d*-fenfluramine (45). In addition, two studies using [¹⁸F]fluorodeoxyglucose (FDG) positron emission tomography (PET) reported low FDG utilization after *d,l*-fenfluramine challenge in frontal areas of the brain (51) and low FDG utilization after *m*-chlorophenylpiperazine challenge in the anterior cingulate in patients with personality disorders who met research criteria for intermittent explosive disorder

compared with healthy comparison subjects (48). A third FDG PET study (52) reported that subjects with intermittent explosive disorder and borderline personality disorder demonstrated a greater relative glucose metabolic rate (rGMR) in the orbitofrontal cortex and amygdala compared with healthy comparison subjects when provoked during a laboratory paradigm of aggression. The observation that healthy subjects demonstrated a lower rGMR in these areas and had a greater rGMR in anterior, medial, and dorsolateral prefrontal regions than subjects with intermittent explosive disorder and borderline personality disorder suggests that brain regions involved in top-down cognitive control of aggression are preferentially activated and deactivated, respectively, in subjects with intermittent explosive disorder and borderline personality disorder compared with healthy subjects (52).

Two ligand binding studies also reported alterations in the binding of ligands for the 5-HT transporter ([¹¹C]McN 5652 [47]) and the 5-HT_{2A} receptor ([¹¹C]MDL100907 BP_{ND} [50]). Reduced 5-HT transporter availability was observed in the anterior cingulate in subjects with intermittent explosive disorder (research criteria) relative to healthy comparison subjects (47). Increased availability of 5-HT_{2A} receptors in the orbitofrontal cortex was noted for subjects with intermittent explosive disorder who had current physical aggression relative to those without current physical aggression and to healthy comparison subjects. Among all subjects with intermittent explosive disorder, 5-HT_{2A} receptor availability was correlated with a state measure of impulsive aggression (50). Finally, a recent functional MRI study demonstrated increased activation of the amygdala and reduced activation of the orbitofrontal cortex in response to angry faces in subjects with intermittent explosive disorder compared with healthy comparison subjects (53).

Taken together, these findings provide neurobiological support for the presence of serotonergic abnormalities globally and specifically in areas of the limbic system (the anterior cingulate) and in the orbitofrontal cortex in individuals with intermittent explosive disorder. These findings also highlight important differences between subjects with intermittent explosive disorder and healthy comparison subjects in differential activation of cortico-limbic structures when stimulated with angry faces (53) or provoked to anger (52) and in an uncoupling of cortico-limbic function (53, 54) in subjects with intermittent explosive disorder.

Treatment Studies

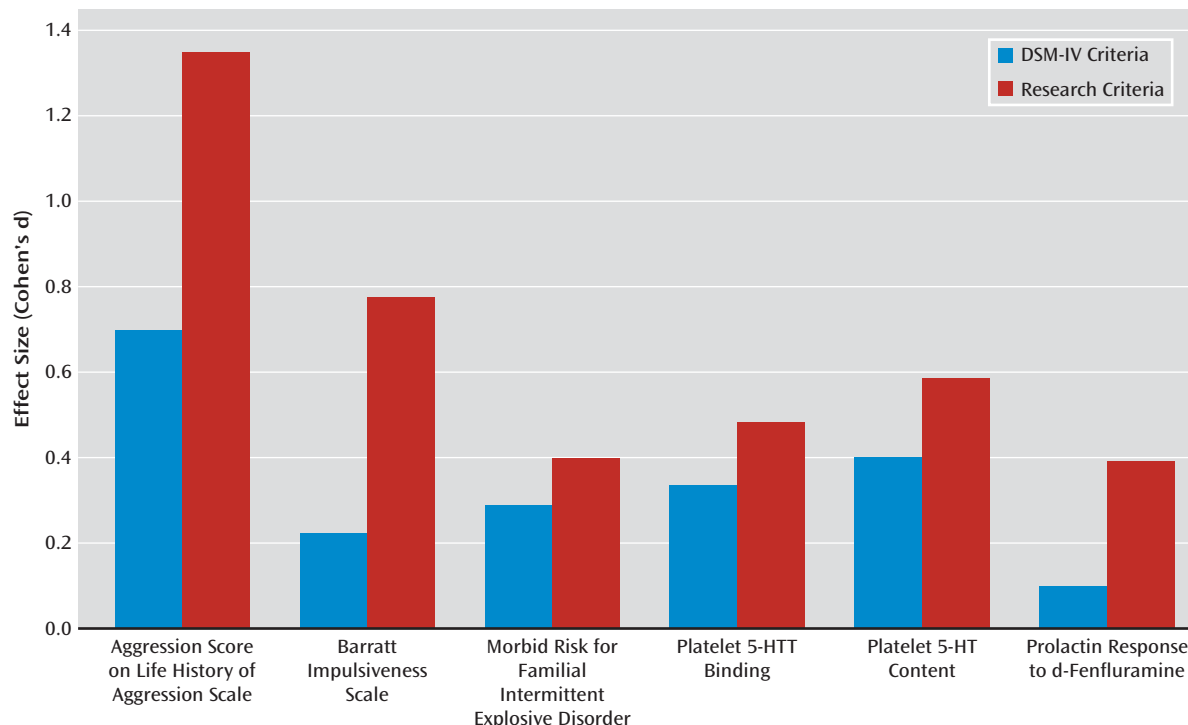
Double-blind placebo-controlled clinical trials in patients with impulsive aggression and/or intermittent explosive disorder (research criteria) have been conducted over the past decade. The first studies reported a reduction in impulsive aggressive behavior with fluoxetine treatment in patients with personality disorders who had intermittent explosive disorder (11). This finding was repli-

cated in two other studies using fluoxetine in subjects with intermittent explosive disorder (55) and in partner-abusing subjects with significant histories of aggression (56). Another study found that divalproex reduced impulsive aggression in patients with cluster B personality disorders with intermittent explosive disorder (57). In other studies, a significant reduction in impulsive aggression was observed in subjects with DSM-IV intermittent explosive disorder treated with oxcarbazepine (58), but not in subjects with intermittent explosive disorder (research criteria) treated with levetiracetam (59). The only study to date of cognitive-behavioral therapy (CBT) (compared with a waiting list condition) in intermittent explosive disorder (research criteria) (5) demonstrated that impulsive aggression, anger, and hostile automatic thoughts were significantly reduced by a CBT package that included relaxation training, cognitive restructuring, and coping skills training. Fluoxetine (11) demonstrated a similar therapeutic response (≥50% reduction in state aggression: 65% for fluoxetine and 70% for CBT; rates of full remission from intermittent explosive disorder [research criteria] criterion A symptoms: 29% for fluoxetine and 33% for CBT). Notably, subjects in the two studies had similar mean Life History of Aggression scores (18 [SD=5] for fluoxetine and 19 [SD=4] for CBT). Given that these two treatments likely work through different mechanisms, combination of the two modalities may be more effective than either alone. Further studies are needed to explore this hypothesis.

Future Directions: Intermittent Explosive Disorder in DSM-5

The use of research criteria for intermittent explosive disorder clearly increases the number of individuals who may be given the diagnosis (9, 10), which is to be expected since the research criteria were designed to describe a more inclusive group of individuals with recurrent, problematic, impulsive aggression. However, close examination of our data sets lends deeper support for the use of the research criteria rather than the DSM-IV criteria for intermittent explosive disorder. As shown in Figure 4, the use of the research criteria identifies a group with significantly greater differences in Life History of Aggression scores, Barratt Impulsiveness Scale scores, morbid risk for familial intermittent explosive disorder (38), numbers of platelet 5-HT transporter binding sites (46), platelet 5-HT content (60), and magnitude of physiological response to central stimulation of 5-HT receptors by *d*-fenfluramine (45) compared with subjects without the disorder. The difference in effect size between the two criteria sets was medium to large for scores on the Life History of Aggression scale (0.73 standard deviations) and the Barratt Impulsiveness Scale (0.50 standard deviations) and small to medium for morbid risk of familial intermittent explosive disorder (0.20 standard deviations) and the three biological measures (mean=0.21 standard deviations, SD=0.08;

FIGURE 4. Differences in Effect Sizes for Various Measures in Subjects With or Without Intermittent Explosive Disorder Using DSM-IV or Research Criteria^a



^a Data are from four studies (38, 45, 46, 60). For the Life History of Aggression scale and the Barratt Impulsiveness Scale, data were from all psychiatric subjects in all four studies. Morbid risk of familial intermittent explosive disorder was assessed in Coccaro (38); platelet 5-HTT binding was assessed in Coccaro et al. (46); platelet 5-HT content was assessed in Goveas et al. (60); and physiological response to central stimulation of 5-HT receptors by *d*-fenfluramine was assessed in Coccaro et al. (45). Among subjects assessed for intermittent explosive disorder using the research criteria, $p < 0.05$ on all measures for differences between those meeting and those not meeting criteria. Among subjects assessed by the DSM-IV criteria, $p < 0.05$ only for differences in Life History of Aggression score between those meeting and those not meeting criteria; there were no significant differences on other measures.

range=0.15–0.29). This is because the research criteria, compared with the DSM-IV criteria, identify more individuals who are highly impulsive aggressive and who simultaneously demonstrate the expected biogenetic correlates of impulsive aggression.

The research criteria have also been used as a template to attempt to distinguish children and adolescents with aggression and irritability from those who have similar symptoms but have bipolar disorder. This is a critical and important step for the field of child and adolescent psychiatry. Research in this area has been taking place over the past decade and is expected to lead to a new diagnosis—disruptive mood dysregulation disorder—in which aggressive outbursts are conceptualized as a mood disorder (61) rather than as an impulse control disorder. While adults with intermittent explosive disorder (however defined) have a significant history of disruptive behavior disorders in childhood, there are no available data to speak to the continuity of disruptive mood dysregulation disorder in childhood and adolescence and intermittent explosive disorder in adults. Accordingly, research will be needed to determine which children and adolescents have intermittent explosive disorder or disruptive mood dysregulation disorder.

Conclusions

Research findings underlying the validity of intermittent explosive disorder come from multiple data sets that consistently show that, however defined, it is a commonly prevalent disorder across studies and countries, with similar phenomenological characteristics, important neurobiological findings, and documented responsiveness to treatment. These data suggest substantial diagnostic validity for intermittent explosive disorder that is sufficient for recognition and inclusion in DSM-5.

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Clinical Guidance: Intermittent Explosive Personality Disorder

Intermittent explosive personality disorder, first introduced in DSM-III, has now received more intensive research and clinical characterization, according to Coccaro. The disorder consists of either high-intensity outbursts of aggression occurring several times yearly or less intensive outbursts several times monthly, a more treatable form. The disorder begins in adolescence or early adulthood; prevalence is about 5%. It appears to be separate from childhood disruptive behavioral disorders, such as conduct disorder and oppositional defiant disorder. Fluoxetine and cognitive-behavioral therapy together appear to have synergistic treatment effects.