

## Intermittent Explosive Disorder

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*Here: a close up look at impulsive aggression.*

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 (IED) and was thought to be rare. However, DSM criteria for IED were poorly operationalized and empiric research in IED was limited until the past decade, when research criteria were first developed.<sup>1</sup> Subsequently, interest in disorders of impulsive aggression led to a series of epidemiological studies that documented IED to be as common as several other psychiatric disorders.

Other recent research indicates that criteria for IED best identifies a group of individuals with robust differences in clinical characteristics, neurobiological findings, and documented responsiveness to treatment. In addition, other data strongly suggest important delimitation from other disorders previously thought to obscure the diagnostic uniqueness of IED. These data, across many studies by a variety of investigators, led to newly revised criteria for IED in DSM-5.

[[{"type":"media","view\_mode":"media\_crop","fid":"33297","attributes":{"alt":"Intermittent Explosive Disorder","class":"media-image media-image-right","id":"media\_crop\_3920932135372","media\_crop\_h":"0","media\_crop\_image\_style":"-1","media\_crop\_w":"100","title":"\u00a9 Shutterstock.com","typeof":"foaf:Image}}]]What is impulsive aggression?

Human aggression constitutes a multidetermined act that results in physical (or verbal) injury to self, others, or things. It appears in several forms and may be defensive, premeditated (predatory), or impulsive (nonpremeditated). When recurrent in



frequency, the latter two forms are psychopathological. A converging pattern of data consistently points to critical differences between impulsive and premeditated aggression such that while the two may appear in the same individual at different times, the underpinnings of the two are quite different.<sup>2,3</sup>

Because this article is confined to IED as defined in DSM-5, the focus is on impulsive aggression. The most critical aspect of this phenomenon is that acts of impulsive aggression represent a quick and typically angry response nearly always triggered by a social threat or frustration that is out of proportion to the situation. These aggressive acts may include verbal arguments, temper tantrums (with or without property damage or harm to others), property assault, or assault on people or animals. In fact, the severity of the aggressive outburst is less relevant than the fact that the aggressive behavior is "explosive." Other important DSM-5 criteria specify that most of the aggressive outbursts are impulsive, cause distress to the individual or impairment in the psychosocial function of the individual, and are not due to another disorder (ie, do not occur exclusively during another disorder).

### **Epidemiology of IED**

The National Comorbidity Survey Replication (NCS-R) reported a lifetime prevalence of IED in the US of 7.3% by "broad [DSM-IV] criteria" and 5.4% by "narrow criteria," and past year prevalence of 3.9% and 2.7%, respectively.<sup>4</sup> Inspection of the data reveals meaningful differences between the two IED types, with "narrow" IED being far more severe than "broad" IED.<sup>5</sup> "Broad" IED stipulates only 3 aggressive outbursts during a lifetime; "narrow" IED requires at least 3 aggressive outbursts in a year.

DSM-5 criteria include both non-injurious and non-destructive aggressive outbursts, provided that they are quite frequent (ie, average of 2 outbursts per week for at least 3 months). The number of DSM-5 IEDs in the US is uncertain; however, a review of the raw data from the NCS-R study suggests that the lifetime prevalence of DSM-5 IED is likely to be between 2% and 3%.

### **Psychiatric comorbidity**

Because impulsive aggressive behavior appears in patients with many diagnoses, most clinicians have been reluctant to make a diagnosis of IED in the absence of other psychiatric diagnoses. In fact, impulsive aggressive behavior is manifest in all humans early in life and before the onset of other psychiatric disorders. In the vast majority of people, impulsive aggressive behaviors

diminish over time, frequently well before adolescence.<sup>6</sup> In the adolescent supplement to the NCS-R, lifetime prevalence of DSM-IV IED by “narrow” criteria was 5.3%, similar to what was found in adults.<sup>7</sup>

Clinical studies suggest significant comorbidity of IED with mood disorders, anxiety disorders, and substance use disorders. In each case, with the exception of phobic anxiety disorders, the age of onset of IED is reported to be earlier than that of the comorbid disorder. This suggests independence of the disorders or that IED might be a risk factor for the comorbid disorder. A similar finding was found in a family history study of IED.<sup>8</sup> Some argue that the diagnosis of IED should not be made in the presence of borderline personality disorder (BPD) or antisocial personality disorder (ASPD). However, when examined empirically, levels of lifetime aggressive behavior among “BPD/ASPD only” individuals are markedly lower than those among persons who also meet criteria for IED, indicating that both diagnoses should be made when criteria for both are met.<sup>1</sup>

### **Medical comorbidity**

There has been evidence for the association between impulsive aggression, and/or irritability, and cardiovascular morbidity for many years. A reanalysis of a large community data set has confirmed this relationship for DSM-IV IED.<sup>9</sup> Specifically, the study noted that in individuals with IED, there is an increased risk of coronary heart disease; hypertension; stroke; diabetes; arthritis; ulcer; headaches; and back/neck pain and other chronic pain. Another study reports a significant correlation between IED and diabetes.<sup>10</sup>

A factor tying many of these conditions (eg, coronary heart disease, stroke, arthritis, ulcer) together may be abnormalities of immune function. A study found that levels of plasma inflammatory markers (C-reactive protein [CRP] and interleukin-6 [IL-6]) were higher in individuals with IED than in psychiatric and healthy controls.<sup>11</sup> Moreover, a history of aggressive behavior has been shown to directly correlate with levels of CRP and IL-6. It is not known if these elevations are causal to aggression as suggested by animal studies or merely associated with aggressive behavior.<sup>12</sup> In either case, additional studies are needed to determine whether there is a rationale to treat the low-grade inflammation that may be present in individuals with IED.

### **Developmental and familial correlates**

IED appears in childhood and peaks in adolescence: studies of adults report the mean age of onset as the mid-teens<sup>4</sup>; studies

of adolescents report the mean age of onset at about 12 years.<sup>7</sup> The average duration of IED ranges from more than 10 years to nearly the whole lifetime, which suggests a persistent and chronic course without treatment. A recent family history study reported that first-degree relatives of individuals with IED (probands) have about a 34% chance of also having IED compared with about 10% in controls.<sup>8</sup> The increased familial risk of IED was not affected by comorbidity in the probands or in the individual relatives. This is consistent with observations from twin studies that report moderate degrees of genetic influence underlying measures of both aggression and impulsivity.<sup>13</sup>

### **Psychosocial antecedents**

A history of trauma in childhood has long been thought to be associated with the development of aggression later on in childhood and in adolescence.<sup>14</sup> While few studies have been published in the area of IED, one community survey reported a significant association between DSM-IV IED in a South African sample.<sup>15</sup> The findings indicate that trauma was more common among those with “narrow IED” who had a history of trauma associated with a crime, trauma to a close friend or family member, and multiple trauma (ie, 6 or more episodes).

Nickerson and colleagues<sup>16</sup> reported that interpersonal traumas and traumas experienced early in life are particularly predictive of IED. A recent study showed higher scores on the Childhood Trauma Questionnaire (CTQ) and lower scores related to parental care in DSM-5 IED subjects than in both psychiatric and healthy controls.<sup>17,18</sup> Notably, CTQ scores were correlated with hostile attribution bias scores that were significantly greater in individuals with DSM-5 IED.<sup>17,19</sup> This is consistent with data that strongly suggest that trauma/maltreatment in childhood is associated with aggression in later childhood or adolescence and that this relationship is mediated by hostile attribution bias.<sup>14</sup> While we may not be able to prevent trauma/maltreatment in childhood, it may be possible to intervene at the level of attribution bias and to reduce the propensity to be impulsively aggressive at a later time in life.

### **Sociodemographic correlates**

Clinical studies of IED suggest a male to female ratio of about 2 to 1. This is only partially supported by data from community samples in which only a small number of studies report an excess of males to females (odds ratio = 1.4 to 2.3).<sup>5</sup> Other sociodemographic factors (eg, age, race, education, marital

status, occupational status, family income) indicate variable and only modest correlates with IED.<sup>5</sup>

### **Psychological correlates**

Not surprisingly, individuals with IED demonstrate abnormalities in a number of psychological areas. Compared with controls, individuals with IED have:

- Elevations of relational aggression aimed at damaging interpersonal relationships<sup>20</sup>
- Elevations of hostile attribution bias, and negative emotional responding, to socially ambiguous stimuli<sup>19</sup>
- Elevations of affective lability and affective intensity<sup>21</sup>
- Immature defense mechanisms, including acting out, dissociation, projection, and rationalization<sup>5</sup>

Most recently, individuals with IED have been reported to have reduced emotional intelligence.<sup>22</sup> All of these abnormalities provide a rationale for psychological intervention, particularly those that focus on emotional and social information processing.

### **Neurobiological correlates**

Neurobiological studies clearly show a bio-behavioral relationship between aggression and select brain chemicals, such as serotonin. Persons with IED are reported to have altered serotonin function compared with persons without IED, as evidenced by a reduction in the number of platelet serotonin transporters or in the magnitude of the prolactin response to the serotonin agent fenfluramine.<sup>23,24</sup> Positron emission tomography studies report lower fluorodeoxyglucose utilization after fenfluramine in the frontal areas of the brain and lower fluorodeoxyglucose utilization after meta-chlorophenylpiperazine challenge in the anterior cingulate in IED/BPD subjects than in healthy controls.<sup>25,26</sup>

Two ligand-binding studies have also reported alterations in the binding of ligands for the serotonin transporter and the serotonin 2a receptor.<sup>27,28</sup> Serotonin transporter availability in the anterior cingulate was less in IED subjects than in controls; availability of serotonin 2a receptors in the orbitofrontal cortex was greater in IED subjects with current physical aggression than in those without current physical aggression and in healthy control subjects.

A functional MRI study showed that IED subjects had increased activation of the amygdala and reduced activation of the

orbitofrontal cortex to angry faces compared with controls.<sup>29</sup> Recent volumetric studies have also noted reduced gray matter volume in the orbitofrontal cortex, the medial prefrontal cortex, the anterior cingulate cortex, the insula, and the amygdala in IED subjects compared with controls.

### Treatment

Double-blind, placebo-controlled, clinical trials in patients with impulsive aggression and/or IED have been conducted over the past decade. A reduction was seen in impulsive aggressive behavior after fluoxetine treatment in personality-disordered patients with IED.<sup>30,31</sup> This was replicated in 2 other studies of fluoxetine.<sup>32,33</sup> In another study, patients with cluster B personality disorder who had IED and were treated with divalproex were found to have a reduction in impulsive aggression.<sup>34</sup> A significant reduction in impulsive aggression was seen with oxcarbazepine.<sup>35</sup> Levetiracetam had no effect on aggression.<sup>36</sup>

In a study of cognitive-behavioral therapy (CBT) versus wait-list control, impulsive aggression, anger, and hostile automatic thoughts were significantly reduced with CBT that included relaxation training, cognitive restructuring, and coping skills training.<sup>37</sup> Fluoxetine and CBT had similar therapeutic responses (greater than 50% reduction in state aggression). Given that both modalities are likely working through different mechanisms, the combination of the two modalities may be more effective than either one alone. Further studies are needed to explore this hypothesis in a head-to-head comparison of these interventions.

### Disclosures:

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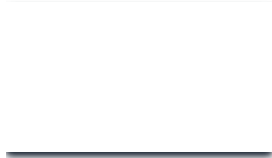
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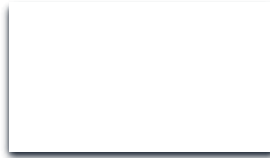
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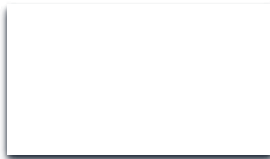


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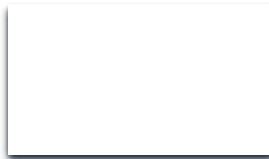


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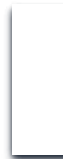
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