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Intermittent Explosive Disorder
Epidemiology, Diagnosis and Management

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Abstract

Intermittent explosive disorder (IED) is characterised by discrete episodes of aggressive impulses that result in serious assaultive acts towards people or destruction of property. IED causes severe impairments in daily function. The diagnosis of IED should be made only after a thorough medical work-up. A structured or semi-structured diagnostic interview is helpful to ensure that comorbid and pre-existing conditions are considered.

There is a lack of controlled trials of agents for the treatment of patients with IED, but there is evidence that mood stabilisers, antipsychotics, β-blockers, α_2-agonists, phenytoin and antidepressants may be useful. Behavioural interventions may be valuable as part of the overall treatment of IED.

Intermittent explosive disorder (IED) is characterised by discrete episodes of aggressive impulses, which are grossly out of proportion to the precipitating psychosocial stressor, that result in serious assaultive acts towards people or destruction of property.[1] Despite substantial evidence identifying impulsive aggressive behaviour in children, adolescents and adults,[2-5] there are few studies of patients who have been rigorously diagnosed as having IED. Nevertheless, many physicians are faced with the task of treating these impulsively aggressive patients. The purpose of this article is

to aid physicians in assessing these patients and in making the diagnosis, as well as in the pharmacological management of IED.

1. Neuropathophysiology

Based on animal models, impulsive aggression is thought to be primarily defensive in nature, driven by fear, anger and cognitive distortion of environmental circumstances, with high levels of autonomic arousal.[4] Adults with IED consistently describe their aggression as defensive, as an 'adrenaline rush' and as having a high affective component.[6]

Neurobiological studies of aggression suggest that numerous neurotransmitters are involved. The most consistent findings suggest disruption in the serotonergic system. In particular, low CSF levels of 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, have been reported in impulsive, violent patients.[2,7-10] Studies of the catecholamine system in aggressive patients have been inconclusive, largely because of the complexity of the system.[11,12] In addition, elevated levels of testosterone have been associated with aggression in adults and postpubertal adolescents.[13-15]

The interactions between neurotransmitters underscore the difficulty in understanding behaviour based on neurotransmitter systems. For example, serotonergic neurons project throughout the brain, including to areas rich in dopaminergic neurons (ventral tegmental area, substantia nigra), where serotonin has a largely inhibitory effect on dopamine and noradrenaline (norepinephrine). These neurons also project through the limbic system, the spinal cord intermediolateral cell column, which controls sympathetic outflow, and the hypothalamus, which modulates numerous hormonal releasing factors.[11] Anatomical evidence suggests that the prefrontal cortex and amygdala are associated with impulsive aggression.[16]

2. Diagnostic Criteria

The current DSM criteria for IED are outlined in table I. Throughout the years, the DSM definition of IED has changed,[17] which has hindered the development of research tools and the acceptance of the diagnosis in the field. Furthermore, it is hard to ascertain from the literature how many patients identified as having 'impulsive aggression' meet the current DSM-IV definition of IED. Many studies of aggressive individuals either do not specify diagnoses or use non-DSM definitions such as 'rage attacks' and 'episodic dyscontrol'.[18,19]

The DSM-IV notes that neurological conditions may be present (i.e. head injury, loss of consciousness, seizures) with IED, but if the clinician judges that the aggressive acts are direct effects of these conditions, a 'personality change due to a general medical condition' diagnosis should be used. Additionally the DSM-III[21] and DSM-III-R[22] versions excluded individuals with signs of generalised impulsive aggression between episodes as well as those who met criteria for borderline personality disorder and antisocial personality disorder. The current criteria allow for other disorders with the caveat that their aggressive acts are 'not better accounted for by another mental disorder'.[1] For example, aggression in incarcerated adolescents and adults has been classified as either proactive (predatory) or reactive (impulsive).[23,24] Barratt et al.[24] differentiated impulsive from nonimpulsive antisocial incarcerated adults using event-related potentials (ERPs), treatment response to phenytoin and neuropsychological measures. The additional diagnosis of IED could therefore give a much clearer picture of the patients' needs.

Table I. DSM-IV criteria for intermittent explosive disorder[20] (reprinted with permission from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, copyright 2000 American Psychiatric Association)

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 psychosocial stressor
C.	The aggressive behaviours are not better accounted for by another mental disorder and are not the direct physiological effect of a substance or general medical condition

3. Epidemiology

The DSM-IV notes, 'IED is apparently rare'. However, because the definition of IED has changed through the years, estimates from past studies are difficult to compare. Monopolis and Lion[25] used a chart review of 830 hospitalised patients to estimate the incidence of IED. They found that 2.4% of patients were given the diagnosis of IED; however, upon closer review, only 1.1% of these patients fulfilled the documented diagnostic criteria outlined in the DSM-III. Felthous et al.[26] systematically evaluated 433 men with histories of aggression. Of these men, only 1.8% met full DSM-III criteria for IED. Coccaro et al.[27] assessed 188 patients with comorbid personality disorders and histories of aggression using a structured interview and found that 25% met DSM-IV criteria for IED.

Using the Minnesota Impulsive Disorders Interview, Lejoyeux et al.[28] noted that 24% of 79 inpatients who met criteria for alcohol dependence also met DSM-IV criteria for IED. Zimmerman and Mattia[29] reported a prevalence of 4.5% for IED using the Structured Clinical Interview for DSM-IV (SCID) in 400 psychiatric outpatients. Coccaro[17] examined a data set by Zimmerman et al.[30] of 748 psychiatric outpatients. He estimated a diagnosis of IED in 6.5% of this sample, with a community rate of approximately 1 to 2% for the disorder. Zimmerman and Posternak[31] noted that of 1300 psychiatric outpatients interviewed using the SCID, 40 were diagnosed as currently having IED, yielding a point prevalence of 3.1%.

In a literature review of impulse control disorders, McElroy et al.[32] noted that IED or episodic aggressive outbursts often begin in childhood, adolescence or early adulthood and follow a chronic course. In 27 patients who met DSM-IV criteria for IED, 75% reported that their explosive behaviour began in adolescence, with a mean age of onset of 14 years and a mean duration of 20 years.[6]

4. Assessment

The diagnosis of IED should be made only after a thorough medical work-up has been completed, including a physical/neurological examination and a careful review of the patient's history and medical record. Consultation with a neurologist is helpful in many cases to assist with exclusionary diagnoses such as histories of head injury, memory loss and seizures, as well as findings on neurological examinations.[6,19] An EEG, computed tomography (CT) or magnetic resonance imaging (MRI) scans and neuropsychological testing should be ordered when indicated.

A structured or semi-structured diagnostic interview is helpful to ensure that comorbid and preexisting conditions are considered. Robins and Novaco[33] note that individuals with severe anger may not be objective informants of their behaviour. We recommend the use of multiple informants, especially family members, to accurately report the precipitants, duration and quality of the outbursts.

As there is a high degree of psychiatric comorbidity with IED,[6] the greatest challenge facing a clinician is determining whether the aggression is not better accounted for by another mental disorder. The DSM has many diagnoses associated with aggression. Pabis and Stanislav[34] list 24 DSM-IV diagnoses that have aggression as a primary diagnostic criterion or an associated feature, including such disorders as mental retardation, autism and dissociative disorders where aggression may be an associated syndrome. We have narrowed this list to those where aggression may be a core diagnostic symptom (table II). In addition, mood disorders and psychotic disorders can have irritability and aggression as manifestations of the primary disorder.

We recommend the use of a graphic timeline for the onset of aggression and comorbid psychiatric diagnoses. As described by Post et al.,[35] the timeline includes a patient's major psychiatric disturbances, as well as significant life events, listed on the horizontal axis. The severity of each illness is rated on the vertical axis and a parallel line notes

Table II. DSM-IV diagnoses where aggression is an explicit criterion (reproduced from Pabis and Stanislav,[34] with permission)

Intoxication with alcohol, amphetamines, cocaine, inhalants, phencyclidine, sedatives, hypnotics or anxiolytics
Antisocial personality disorder
Borderline personality disorder
Conduct disorder
Dementia (Alzheimer's type or other aetiology) with behavioural disturbance
Intermittent explosive disorder
Oppositional defiant disorder
Personality change caused by a general medical condition, aggressive type
Post-traumatic stress disorder

treatment modalities and medications. The significant life events can be modified depending on the particular person (i.e. to include when substance abuse began, and when incarcerations, deaths, etc. occurred). This graph aids in clarifying when aggressive events occurred and whether they could be attributed to something other than IED.

The interview module for IED (IED-M)[27] attempts to empirically study IED and refine the diagnosis based on inclusionary and exclusionary criteria focusing on frequency of outbursts, level of aggression and level of social impairment. The IED-M requires a minimum number of episodes over time (twice a week for 1 month). The episodes must be impulsive and clearly excessive to the given provocation. The IED-M also requires the specific presence of distress associated with the aggressive behaviour.

In their study of IED in adults with personality disorders, Coccaro et al.[27] used 'revised criteria', whereby episodes of severe verbal aggression were included for meeting criteria for the diagnosis. In this study, the patients with IED had higher scores on measurements of aggression and impulsivity than individuals with personality disorders who did not meet criteria for IED. In addition, these patients had more current Axis I diagnoses, especially depression and dysthymia.[27] We administered the IED-M to children and adolescents (between the ages of 10 and 17 years).[36] Patients classified with IED had significantly more documented episodes of physical aggression while in residential treatment and reported more lifetime aggression compared with psychiatric control individuals. In addition, these patients reported more lifetime aggression and scored higher on measures of oppositionality, inattention and hyperactivity/impulsivity compared with community control individuals. These patients exhibited a significantly higher number of DSM-IV IED symptoms.

5. Psychopharmacological Intervention

There is a lack of controlled trials concerning the pharmacological treatment of patients with IED. However, the literature on the treatment of aggressive behaviour provides some evidence for the use of mood stabilisers, phenytoin, selective serotonin reuptake inhibitors (SSRIs), β-blockers, α_2-agonists and antipsychotics in curbing impulsivity and aggression.[34,37,38]

5.1 Mood Stabilisers

Lithium has been shown to reduce aggression in a wide range of patient populations, including inmates and patients with psychosis, mental retardation and brain injury.[34,39] In McElroy's[40] open study, ten patients with IED and comorbid manic or mixed bipolar symptoms were started on either lithium (two patients) or valproate semisodium (divalproex sodium) [eight patients]. 'Responders' were defined as having a greater than 50% reduction in IED symptoms. One of two patients (50%) responded to lithium and six of eight patients (75%) responded to valproate semisodium.

In a double-blind study, Sheard et al.[41] found lithium to be superior to placebo in reducing aggressive outbursts in 66 older adolescent and young adult prisoners (mean age 19.4 years, mean dosage 1514 mg/day, mean plasma concentration 0.78 mmol/L). In two double-blind, placebo-controlled studies of hospitalised children (aged 5 to 12 years) with treatment-resistant aggressive conduct disorder, Campbell et al.[42,43] found lithium carbonate to be superior to placebo for reducing problematic behaviours. In a placebo-controlled, double-blind

study, Malone et al.[44] found that, in 28 children and adolescents (mean age 12.69 years), treatment response to lithium was associated with a more 'affective' and less predatory subtype of aggression (45% were considered responders). In a further study, Malone et al.[45] administered lithium (mean dosage 1425 mg/day, mean plasma concentration 1.07 mmol/L), in a double-blind, 6-week, placebo-controlled trial, to adolescents with conduct disorder. They noted a significant decrease in aggression as well as general clinical improvement in patients receiving lithium compared with those receiving placebo.

Despite few controlled studies, valproate semisodium has been used to decrease aggression in adults with dementia, borderline personality disorder, schizophrenia, brain injury and mental retardation.[46] A double-blind, controlled comparison of lithium, valproic acid (sodium valproate) and placebo examined hostile, impulsive and aggressive behaviours in 179 adults with bipolar disorder. Valproic acid was superior to lithium and placebo in reducing these behaviours in patients in the manic phase.[47]

Donovan et al.[48] reported a decreased number of outbursts and lability in ten disruptive adolescents when they were treated with valproate semisodium in an open trial. In this study, all of the patients had had temper outbursts on a chronic basis for more than 2 years and a diagnosis of either oppositional defiant disorder (ODD) or conduct disorder. These findings were replicated in a double-blind, parallel-group, placebo-crossover study[49] of 20 outpatient adolescents without bipolar disorder but with ODD or conduct disorder and problematic temper and mood lability. These patients were placed on valproate semisodium (dosage range 750 to 1500 mg/day, mean blood concentration 82.2 mg/L). The authors reported significant improvement from baseline measures of aggression and hostility in over 80% of the drug-treated group compared with 25% of the placebo group. All of the placebo responders had finished a 6-week trial on valproate semisodium, suggesting possible extended effects of the drug.

Carbamazepine has been reported to decrease aggression in patients with numerous psychiatric diagnoses.[50] Open studies report decreased aggression in assaultive patients with underlying organicity.[51] Mattes[52] and Mattes et al.[53] reported decreased aggression in patients receiving carbamazepine in two open studies. Although these studies included a variety of patients, 19 of 34 and 12 of 28 patients, respectively, were classified as having IED.

In an open trial reported by Hakola and Laulumaa,[54] carbamazepine decreased aggression in eight women with violent episodic outbursts. Neppe[55] found improved behaviour in 9 of 13 patients receiving carbamazepine in a double-blind, randomised, within-subject study. Patients receiving placebo had overt aggression rated as twice as severe and 1.5 times as common. In both of these reports, the patients had abnormal findings on EEGs but did not have epilepsy.

A small, double-blind study (n = 4) found decreased aggression and improved cognitive function in patients with frontal lobe dysfunction while receiving carbamazepine.[56] In an open pilot study, Kafantaris et al.[57] reported significant improvement – in terms of fighting, temper outbursts and temper tantrums – using carbamazepine in patients with conduct disorders described as highly aggressive and explosive. However, these results were not replicated in a controlled trial by Cueva et al.,[58] which showed no significant effect on a rating of aggression in patients receiving carbamazepine versus those receiving placebo.

5.2 Phenytoin

Phenytoin has been used in a double-blind, placebo-controlled, crossover study[59] of 60 inmates who displayed aggressive behaviour. Only those classified as having impulsive aggression responded to a fixed dose regimen of phenytoin 200mg every morning and 100mg every evening, with a threshold of improvement at blood concentrations over 4 to 5 μg/L.

Stanford et al.[60] used phenytoin in a double-blind, placebo-controlled, crossover study that in-

volved 23 patients who met criteria A and B for IED (see table I). Patients receiving phenytoin had significantly fewer aggressive outbursts per week compared with their baseline and with individuals receiving placebo. In addition, drug-treated patients had significantly lower scores on tension/anxiety, depression/dejection and anger/hostility sections of the Profile of Mood Status. This study did not provide a DSM-IV Axis I diagnosis, but noted that all patients met criteria for a DSM-IV personality disorder.

5.3 Selective Serotonin Reuptake Inhibitors

Given the high degree of overlap between IED and affective symptoms, and the data suggesting dysregulation of the serotonin system in IED (see section 1), it is not surprising that SSRIs have been used in the treatment of this disorder.[27,40,61]

In a double-blind, placebo-controlled trial of fluoxetine in 40 patients with personality disorders, Coccaro and Kavoussi[62] report reduced scores on the irritability and aggressive subscales of the Overt Aggression Scale-Modified for Outpatients (OAS-M) and improved scores on the Clinical Global Impression (CGI) scale rating of improvement. Coccaro[17] noted that all patients in the fluoxetine study met criteria for IED using 'research criteria', which included episodes of verbal aggression as part of the diagnosis.[27]

Feder[63] described effective treatment of three patients who had IED with sertraline; dosages ranged from 50 to 100 mg/day, with positive effects noted after 2 to 6 weeks of treatment. In an open trial involving 27 patients with IED, 10 received an antidepressant.[40] Of these patients, 50% were considered responders [one to sertraline (n = 3) and four to venlafaxine (n = 5)]. The remaining two patients, who received fluoxetine, showed no response.

5.4 β-Blockers

In a number of case studies, propranolol has been reported to help patients who met DSM-III criteria for IED.[52,64] Further inspection of these papers reveals that many of these patients had experienced some form of brain damage (head trauma, meningitis). In controlled studies,[65,66] propranolol and pindolol have been effective in decreasing aggression in patients with brain damage. However, many of these patients would not meet current criteria for IED as they would be classified by the DSM-IV as having 'changes due to a general medical condition'.

5.5 α_2-Agonists

Kemph et al.[67] showed a significant decrease in aggression against people and property in 17 adolescents in an open trial of the α_2-agonist clonidine. Dosages began at 0.005 mg/day and increased to an effective dose using twice daily administration. The mean effective dosage was 0.4 mg/day. However, there has been increased concern over the use of clonidine because of reports of sudden death in children receiving the drug when combined with other medications.[68,69] Its use has also been limited by the adverse effects of sedation, low blood pressure and worsening depression; in addition, its short half-life can cause rebound, and therefore multiple daily doses are required.

There has been increased interest in guanfacine for reducing target symptoms in adolescents with attention-deficit hyperactivity disorder; however, these studies were open.[70,71] Compared with clonidine, guanfacine seems preferable as it is less sedating, has a longer half-life (usually only twice daily administration is necessary) and is more selective for the α_2-receptor. However, it has not been adequately studied in aggression.

5.6 Antipsychotics

Antipsychotics have been used for the short-term treatment of aggression.[34,72] However, their use in patients with IED, a chronic condition, has been limited by risks such as dystonia, akathisia, tardive dyskinesia, neuroleptic malignant syndrome, cognitive dulling and sedation.[72]

There has been recent evidence of the usefulness of atypical antipsychotics in treating aggression. These agents may prove useful in the long-term treatment of patients with IED, as their unique

chemical properties of dopaminergic and serotonergic receptor antagonism may provide a decreased risk of tardive dyskinesia and extrapyramidal symptoms compared with the typical agents.[73,74]

Buitelaar et al.[75] used risperidone (mean dosage 2.9 mg/day) to control aggression in hospitalised adolescents with low IQs. Using a 6-week, double-blind, placebo-controlled design, they found significant improvement on the CGI severity index in school and on the ward. Using the OAS-M, they noted significantly decreased aggression on the hospital ward. Findling et al.[76] randomly assigned 20 youths with conduct disorder to placebo or risperidone in a 10-week, double-blind study. Risperidone significantly decreased aggression compared with baseline and was superior to placebo by week 7 as measured by the rating of aggression against people and property. Additional studies with these compounds are warranted in patients with IED.

6. Behavioural Interventions

Behaviour management therapy, social skills training, cognitive behaviour therapy (with an emphasis on anger management), group therapy and family therapy have been useful for controlling aggressive behaviour.[77,78]

Edmondson and Conger[78] examined 18 controlled studies of the treatment of anger published between 1970 and 1994. They noted the following effect size (EF) for various treatments: relaxation training (EF = 0.82), social skills training (EF = 0.80), cognitive-relaxation techniques (EF = 0.76) and cognitive behavioural treatment (EF = 0.64). These values are considered medium to large.[79] The authors note, however, that these studies varied in their designs, patients and measures. For example only three of the studies assessed observed aggression as an outcome, two studies using social skills (EF = 1.08) and one study assessing cognitive therapy (EF = 0.34).[78]

These authors discuss anger as a multidimensional framework. They indicate that research and treatment of anger should consider the following issues: antecedents, behavioural response dimensions, cognitive dimensions, physiological responses and the subjective experience of the emotion. A good example of such a treatment is social relations intervention.[80-82] This treatment includes social skills training with a cognitive-behavioural element using individual and small group sessions. The sessions begin with a focus on social problem solving, such as identifying and articulating problems. Patients are taught increased awareness of anger and physiological arousal as cues to begin problem solving. Further training focuses on inhibiting impulsive reactions, considering consequences and generating alternative behaviours. Cognitive interventions include the use of self-statements and reframing interpretations of stressful situations. Additional training helps with body language and negotiation skills.

The controlled studies of social relations intervention in aggressive children have reported improvement on a variety of measures,[80,81] but decreased aggression as an outcome variable was only found in aggressive, socially rejected children.[82] It is therefore difficult to know how to extrapolate these findings to IED, which is a diagnosis defined by acts of aggression, not anger. Further research is needed on patients with IED to delineate the process that leads to aggression in these patients. These techniques have not been systematically studied in patients with IED.

In the case report by McElroy et al.[6] involving patients with IED, three of four patients receiving insight-oriented psychotherapy reported it as helpful, and behaviour therapy was reported as useful in reducing explosive symptoms in one of two patients. Four patients received other forms of therapy (group, couple or family therapy) and none of these patients reported these interventions as helpful.

There is clearly a need for further studies concerning the interaction of client characteristics, especially specific DSM diagnoses, with treatment outcomes.

7. Recommendations and Conclusions

Given the lack of controlled trials for the treatment of patients with IED, we suggest using associated symptoms and comorbidity as guides for treatment. Mood stabilisers would be helpful for those with 'mood swings', manic symptoms (cyclothymia, bipolar I and II disorders) and clear family histories of bipolar disorder. In patients with criminal histories or abnormal EEGs, carbamazepine, valproate semisodium or phenytoin may be useful. Patients with a history of head injuries or with high degrees of autonomic arousal (racing heart, trembling, elevated blood pressure) could be candidates for either β-blockers or α_2-agonists. Atypical antipsychotics could be used to control a patient's behaviour either alone or while a trial of another medication is being initiated. Caution should be used in patients with abnormal EEGs, as antipsychotics can lower the seizure threshold. Patients with clear symptoms of depression or a compulsive quality to their aggression may need an SSRI as part of their regimen. The use of behavioural interventions should be uniquely tailored to suit individual patient needs. Early identification and intervention is warranted.

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