Intermittent Explosive Disorder and Impulsive Aggression: The Time for Serious Study Is Now

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Despite the inclusion of intermittent explosive disorder (IED) in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) for more than 20 years and despite the results of research over the same period demonstrating significant biogenetic and treatment response correlates of its signature behavior, impulsive aggressive behavior, there is still little formal research underway in individuals with IED.

There is little question that impulsive aggressive behavior is important in our society. Many violent crimes are committed impulsively and many of the people who display less visible, noncriminal forms of impulsive aggression suffer important intra- and interpersonal, vocational, and economic consequences of these behaviors. One could even argue that the identification, study, and treatment of impulsive aggressive behavior in IED (an example of behavioral "disinhibition") is as, if not more, important than its polar opposite condition, generalized social phobia (an example of behavioral "overinhibition"), which has received far more attention from the global pharmaceutical industry, which sets the agenda for the development and marketing of therapeutic agents.

Although there is no question about the suffering of individuals with extreme shyness, is there really any question about the disruption to society at large (and in smaller personal networks) referable to impulsive aggressive behavior? Is there really any question as to the adverse impact these behaviors have on the individuals engaging in impulsive aggressive behaviors? If not, why is the clinical field of impulsive aggression, typified by IED, without community advocates, research foundations, endowed chairs for research, or an agent with a US Food and Drug Administration–approved indication for the treatment of this condition? The answer is lack of knowledge, bias, and fear.

Since the publication of DSM-III in 1980, we have been "taught" that IED is a "rare" condition. Given the way IED was defined in DSM-III, however, it is no surprise that IED appears to be "rare." A critical exclusion criterion in DSM-III (and DSM-III-R) was that people with IED did not display generalized impulsivity or aggression in between the most serious, explosive outbursts. If so, DSM-III/III-R was trying to define IED as a condition in which serious explosive outbursts were generally out of character for the person in question. However, because the vast majority of individuals with intermittent, problematic, impulsive aggressive behavior also display smaller, less serious aggressive outbursts in between the very serious ones, very few potentially appropriate individuals could qualify for the DSM-III/III-R IED diagnosis (these are the same types of individuals in whom dimensional correlates with central serotonin function, as well as responses to specific pharmacologic treatments, have since been documented). In addition, the diagnostic criteria for IED are poorly written, specified, and continue to exclude some individuals from the diagnosis (*eg,* patients with borderline or antisocial personality disorder), even when there are only questionable scientific reasons to do so. Accordingly, the very document that did so much to spark research in so many other psychiatric disorders (*eg,* anxiety disorders) crippled IED from the start.

Problems with the DSM conceptualization of IED, however, can now be overcome with the use of more scientifically based research diagnostic criteria, such as those recently developed (and now in use in selected research centers) over the past 5 years. Use of these criteria will allow for much more research and knowledge in this area. For example, it is now becoming clear that IED is much more common than ever thought before. Preliminary estimates suggest that approximately 5% of individuals in the community meet research diagnostic criteria for IED at some time in their lives, with prevalence in the past month estimated at approximately 2%. Contrary to the expectations of some, most of these individuals are *not* involved in the criminal justice system and are *not* that different than those with other behavioral disorders. If these estimates hold up in future research, IED may be more prevalent than bipolar disorder or schizophrenia. In addition to preliminary epidemiologic findings, IED appears to run in

families and appears to do so in a manner that cannot be explained by the presence of comorbid conditions in the proband with IED or in the first-degree family member related to the IED proband. This is consistent with what is already known about the behavioral genetic study of various measures of impulsivity and aggression, which demonstrate that behavioral traits are under moderate degrees of genetic influence. In addition, the onset of IED peaks in mid-to-late adolescence at a time far earlier than the onset of other, later, common comorbid conditions such as mood or substance use disorders, indicating that it is not caused by most comorbid conditions that it may appear with. Most importantly, impulsive aggressive behavior, the hallmark of IED, already has been responsive to selective serotonin reuptake inhibitors, mood stabilizers, and to selected forms of cognitive-behavioral therapy. Accordingly, should there be more interest in IED as target for study and intervention? Yes; yes, if IED was not an externalizing disorder that renders patients with IED "unsympathetic" or as individuals who simply displayed "bad behavior," and yes, if the risk of impulsive aggression did not make the pharmaceutical industry shudder at the thought of endless lawsuits from patients and their "victims" when something "untoward" occurs in a registration trial for a potential anti-aggressive agent.

Unlike many other conditions in psychiatry (or neurology), IED is an externalizing disorder in which the consequential distress of the condition is experienced, primarily, by individuals interacting with the IED patient (*eg*, spouse, friends, co-workers, children, and others). In this situation, the IED patient is viewed as a "perpetrator" and is nearly always portrayed in an extremely unsympathetic light. Partly, this is because of a lack of general understanding about IED and the distress it causes most of those with the disorder, especially as they ultimately experience the consequences of the disorder and partly because the actions of those with IED are viewed as "bad behavior" rather than as belonging to a disorder with identified biologic and treatment response correlates as seen in disorders of mood or anxiety. This issue is not merely academic. The poor light in which IED is viewed severely limits the likelihood that any "celebrity" with IED will come forward to call for more basic and treatment research in this area and, more importantly, to put a "human face" on the disorder to de-stigmatize it. The impact of "celebrities" to advocate for, and to de-stigmatize, a disorder cannot be underestimated. The surge in interest in research and in the treatment of Parkinson's disease, with the activism of notable disease sufferers such as Michael J. Fox, is only a recent compelling example of this principle. Similarly, it is also unlikely that philanthropists will come forward to begin charitable foundations to fund research or treatment programs in this area or to fund endowed chairs for the study of impulsive aggression in our medical schools. As with potential celebrities, it is unlikely, given the current public awareness and attitude about these behaviors, that any potential philanthropist would feel comfortable admitting that he or she, or a member if his/her family, had this disorder.

A related, but separate issue involves the business and legal stance that the pharmaceutical industry takes toward developing agents for the treatment of impulsive aggression. There is no doubt that many pharmaceutical companies consider impulsive aggression as a therapeutic target. However, few companies lack the business will to attempt approval for an indication in this area. First, pharmaceutical companies had difficulty with the Food and Drug Administration on the issue of gaining an indication for treatment of a "symptom." (Although Food and Drug Administration policy does not preclude obtaining an indication for a "symptom" [*eg*, atypical neuroleptics in the treatment of agitation in schizophrenia], it *is* more difficult to develop "acceptable" protocols that target "symptoms" rather than "syndromal disorders.") However, even when pharmaceutical companies see how they may conceptualize impulsive aggression as a disorder such as IED, they typically choose to study it as a symptom across established disorders in order to allow for broader marketing potential. That this strategy may only obscure the treatment efficacy of the agent in question is not generally considered by those sponsoring such trials. Even when raised, this consideration is typically discarded in favor of the gamble that clinical trials with groups of heterogeneous subjects will reveal treatment efficacy even when their power to do so is diminished as a consequence of the study design at outset. More often, decision makers at pharmaceutical companies "pass" on such studies for one or two reasons: 1) the "market" for the treatment of IED is not "large enough" or 2) the development of anti-aggressive agents comes with the potentially unacceptable liability that impulsively aggressive people will do "aggressive things" to others during the trials and that the company will be inundated with lawsuits, if not during registration trials, then later when the drug is approved for IED or the treatment of impulsive aggression in general.

Here we have the quandary. Impulsive aggressive behavior is a socially important behavior associated with injury, damage, and distress to all who come into contact with it. However, few appear to see past the negative image of the "aggressive perpetrator," so that the greater societal attitude is to understand the behavior and that it may be identified as "disordered," with an identified set of biologic characteristics and treatment response options (as opposed to "bad behavior"), and treated. Compounding societal bias is that few in the position to carry the preliminary research of individual investigators into the clinical world at large are willing to take the risks necessary to develop effective strategies to treat the problem. If this sounds a little like the general state of the field of mental health in the 1950s regarding the study and advanced treatment of major psychiatric disorders, it is.

Isn't it time we caught up with the 21st century, and most of the remaining disorders in the DSM, when it comes to understanding and treating the very basic and critical human problem of impulsive aggression? The answer, I hope, is obvious.