17 Antiepileptic Drugs in the Treatment of Impulsivity and Aggression and Impulse Control and Cluster B Personality Disorders

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INTRODUCTION

We review here evidence that suggest that antiepileptic drugs (AEDs) (a.k.a. anticonvulsants) may be effective for the treatment of impulsivity and aggression across a range of psychiatric disorders. AEDs are increasingly used as primary or adjunctive treatments for impulse control disorders (ICDs) and cluster B personality disorders [in particular borderline personality disorder (BPD)]. Thus, in addition to the reviewing the effects of AEDS on the symptoms of impulsivity and aggression across a variety of diagnoses, we will focus on ICDs and BPD. The AEDs valproate (e.g., divalproex sodium), carbamazepine, and lamotrigine have U.S. Food and Drug Administration (FDA) indications for the treatment of bipolar disorder. Other AEDs, like oxcarbazepine, gabapentin, topiramate, levetiracetam, phenytoin, and tiagabine, are often used as mood stabilizers but do not have FDA indication for bipolar disorder. Use of off-label AEDs requires careful monitoring and publication of all significant results, including adverse effects. The choice of specific AED is often dependent on drug-drug interactions and side-effect profile (1). Side effects from AEDs are typically mild to moderate. Although data regarding longer-term safety of the newer AEDs are limited, they may have more desirable side-effect profiles.

Impulsivity and Aggression

Impulsivity and aggression are natural behaviors controlled by brain mechanisms, which are essential for survival in all species. Understanding those mechanisms may lead to targeted treatment strategies for this symptom domain when these behaviors become dysfunctional. The concept of impulsivity covers a wide range of "actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable outcomes" (2). Moeller et al. (3) defined impulsivity as: "a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others." Aggressive behavior has been defined as a verbal or physical act directed against a person or object that can potentially cause physical or emotional harm that occurs in a premeditated or impulsive manner (3,4). The symptoms of impulsivity and aggression are a significant public health problem and can be manifested by self-injurious behavior (SIB), suicide, suicide attempts, substance abuse, accidents (e.g., motor vehicle), domestic violence, assault, and destruction of property (5–10). Intervention can occur at the symptom, syndrome, or behavioral level.

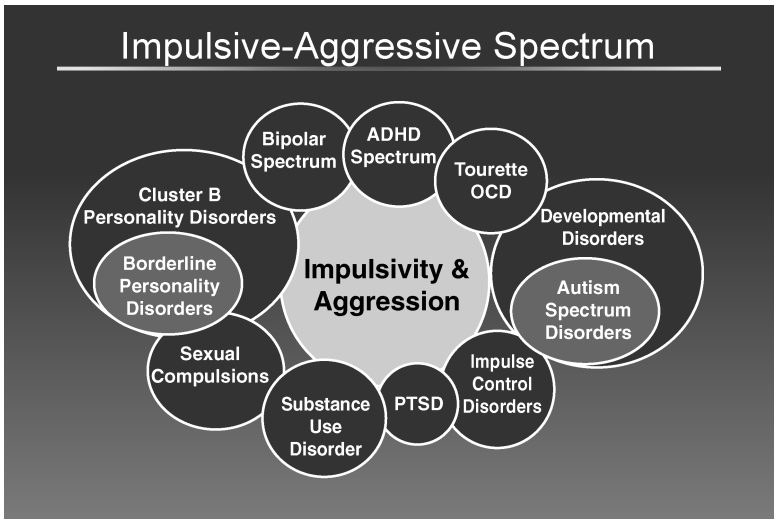

FIGURE 1 Impulsive-aggressive spectrum. *Abbreviations*: ADHD, attention deficit hyperactivity disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder. Q14

Impulsive and aggressive behaviors can be conceptualized as existing on a spectrum where they are the core symptoms of a broad range of psychiatric disorders that are often comorbid with one another, like cluster B personality disorders, ICDs, autism spectrum disorders, and bipolar disorder (Fig. 1). This is based on similarities in associated clinical features (e.g., age of onset, clinical course, comorbidity) and response to pharmacological treatment [e.g., selective serotonin reuptake inhibitors (SSRIs)], suggesting a high degree of overlap among disorders (11). Further, impulsivity can be thought of as part of a compulsive-impulsive dimensional model, where impulsivity and compulsivity represent polar opposite complexes that can be viewed along a continuum of compulsive and impulsive disorders (Fig. 2). One endpoint marks compulsive or risk-aversive behaviors characterized by overestimation of the probability of future harm, exemplified by obsessive-compulsive disorder (OCD). The other endpoint designates impulsive action characterized by the lack of complete consideration of the negative results of such behavior, exemplified by borderline disorder and antisocial personality disorder (ASPD). Anti-impulsive medication classes include SSRIs, serotonin (5-HT)1A agonists, 5-HT2 antagonists (Table 1), lithium, AEDs, atypical and typical antipsychotics, β blockers, α2-agonists (e.g., clonidine, guanfacine), opiate antagonists (e.g., naltrexone), and dopamine agonists (e.g., stimulants, bupropion).

There are many contributing factors to impulsivity and aggression such as genes, gender, environment, psychiatric disorders, and substance abuse. Early environment can alter a person's neurochemistry related to impulsivity and aggression (12). The neurochemistry of aggression and impulsivity may involve serotonin, gamma-aminobutyric acid (GABA), glutamate, norepinephrine, dopamine, androgens, vasopressin, and nitric oxide.

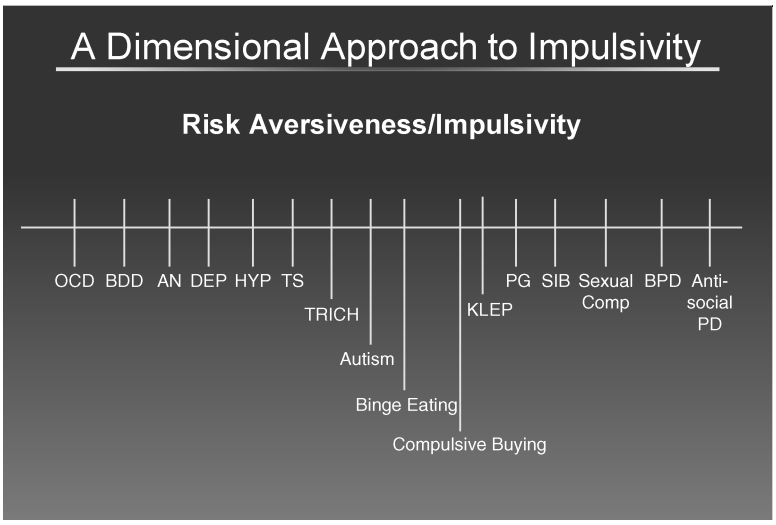

FIGURE 2 A dimensional approach to impulsivity. *Abbreviations*: OCD, obsessive-compulsive disorder; BDD, body dysmorphic disorder; AN, anorexia; DEP, depression; HYP, hypochondriasis; TS, Tourette's syndrome; TRICH, trichotillomania; KLEP, kleptomania; PG, pathological gambling; SIB, self-injurious behavior; Comp, compulsion; BPD, borderline personality disorder; PD, personality disorder.

TABLE 1 Mechanisms of Impulsive Behavioral Disturbances

Serotonin-sensitive	Serotonin-resistant
Low serotonin	Severe arousal
Impulsive aggression	Multiple disturbances
Trait dependent	Mixed-state trait
Increased serotonin function would ameliorate disturbance	Decreased arousal would ameliorate disturbance

Neural Substrates

The orbitofrontal cortex (OFC), with its extensive reciprocal connections with the amygdala (which is implicated in emotional behavior) (13,14), may play a role in correcting or regulating emotional and behavioral responses (15–19). Limbic-orbitofrontal circuit dysfunction may be involved in impulsivity and aggression, at least in a subgroup of patients (20). Impulsivity and aggression may conceivably involve increased limbic discharge, decreased OFC function, and/or hypoactive frontolimbic circuitry (21). Studies suggest that the amygdala and OFC act as part of an integrated neural system, as well as alone, in guiding decision making and adaptive response selection on the basis of stimulus-reinforcement associations (13,22–25). Thus, underactivation of prefrontal areas involved in inhibiting behavior, overstimulation of the limbic regions involved in drive, or a combination of both may result in disinhibited and aggressive behaviors.

For example, in 15 healthy subjects, Pietrini et al. (26) found that compared with imagined scenarios involving emotionally neutral behavior, imagined scenarios

involving aggressive behavior were associated with significant emotional reactivity and reductions in reginal cerebral blood flow (rCBF) in the ventromedial prefrontal cortex (PFC). These results in healthy subjects support previous animal and human studies, which suggest the involvement of the OFC in the expression of aggressive behavior. Reduced serotonergic activity has been associated with impulsive aggression in personality-disordered patients in metabolite, pharmacological challenge, and position emission tomography (PET) studies. In an [^{18}F] fluorodeoxyglucose PET study (27), six impulsive-aggressive patients with intermittent explosive disorder (IED) and five healthy volunteers were evaluated for changes in regional glucose metabolism after administration of d,l-fenfluramine (a serotonergic releasing agent) or placebo. Healthy controls demonstrated increases in glucose metabolism in the orbitofrontal, ventral medial frontal, cingulate, and inferior parietal cortices, while IED patients showed no significant increases in glucose metabolism after fenfluramine in any region. Compared with controls, IED patients also showed significantly blunted metabolic responses in orbitofrontal, ventral medial, and cingulate cortices but not in inferior parietal lobe. These results are consistent with reduced serotonergic modulation of orbital frontal, ventral medial frontal, and cingulate cortices in patients with impulsive-aggressive personality disorders.

OFC [Brodmann area (BA) 10] and ventrolateral PFC (BA 47) activation are thought to exhibit top-down control over limbic pathways (28,29). The amygdala is known to receive major visual input from sensory areas of the cortex, which provide fast responses to simple perceptual and associative aspects of external stimuli (30). Thus, in addition to subcortical pathways of emotional processing, which are thought to act automatically even without awareness of stimuli (31), the OFC and ventrolateral PFC, with their strong interconnections with subcortical areas implicated in emotional behavior, may play a role in correcting emotional responses (15,18,19). In fact, using functional magnetic resonance imaging (FMRI), an abnormal elevation of CBF in the ventrolateral PFC in response to aversive emotional stimuli was found in four of six BPD subjects, but not in controls (29), and was also reported during induced aversive emotional states in patients with anxiety disorders or depression (28). This part of the PFC is directly connected with the basal nucleus of the amygdala, and has been regarded as a gateway for distinctive sensory information, and may modulate or inhibit amygdala-driven emotional responses and thus provide top-down control of the amygdala (28,32,33).

ANTIEPILEPTIC DRUGS AND IMPULSE CONTROL DISORDERS

IED, kleptomania, pyromania, pathological gambling, trichotillomania, and ICDs not otherwise specified (NOS) are the classic disorders of impulse control listed under "impulse-control disorders not elsewhere classified" in the Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision (DSM-IV-TR) (34), in which impulsivity is a core and defining symptom. Further, currently categorized under ICDs-NOS, but proposed to be included as individual ICDs in the DSM-V, are impulsive-compulsive sexual behaviors, shopping, Internet addiction, and excoriation (skin picking). The essential feature of an ICD is the failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others. Additional features include increasing tension or arousal before the act; pleasure, gratification, or relief at the time of the act; and self-reproach or guilt following the act. Impulsivity also plays a significant role in a wide range of other

psychiatric disorders, including mood disorders (particularly mania), personality disorders (borderline and antisocial), eating disorders [e.g., binge eating disorder (BED), bulimia nervosa], substance use disorders, schizophrenia, attention deficit hyperactivity disorder (ADHD), paraphilias, conduct disorder, and neurological disorders with disinhibition.

There is gender predominance for most of the ICDs. Pathological gambling, IED, pyromania, and sexual compulsions are more prevalent in males, whereas kleptomania, trichotillomania, SIB, compulsive shopping, and BED are more prevalent in females. This differential gender distribution indicates that both men and women express impulsivity but do so in different ways. The reasons for this differential gender distribution are unclear but may be related to genetic factors, differences in serotonin turnover, hormonal differences, or social/environmental pressures.

We review here treatment studies of ICDs with AEDs, focusing on pathological gambling as an ICD that may be successfully treated with AEDs.

Pathological Gambling

Pathological gambling has traits in common with many different psychiatric disorders (Fig. 3). The link between pathological gambling and antisocial disorders, including ASPD, conduct disorder, and adult antisocial behavior, is largely determined by genetic propensity. Slutske et al. (35) found that genetic factors account for 61% to 86% of the overlap between antisocial behaviors and pathological gambling and 16% to 22% of the variance for pathological gambling overall. Nonfamilial environmental factors also significantly contribute to pathological gambling and to ASPD and adult antisocial behavior. Antisocial behavior is not just a consequence of pathological gambling but also an independent psychiatric symptom. Further, the risk of alcohol abuse/dependence and adult antisocial behavior overlap, suggesting that impulsivity is a mediator in these conditions. In

FIGURE 3 Pathological gambling. *Abbreviation*: ADHD, attention deficit hyperactivity disorder.

other words, impulsivity can be thought of as a common endophenotype, or nonobvious underlying trait, in these and related psychiatric disorders.

In FMRI studies, researchers observed that, compared with healthy subjects, pathological gamblers have decreased activity in their ventromedial PFC during presentation of gambling cues (36) and during a cognitive inhibition task (e.g., Stroop color-word) (37). The ventromedial PFC is associated with decision making (38), and the OFC plays a role in the processing of rewards during the expectancy and experiencing of monetary gains or losses (17,39–41). In a recent imaging study of pathological gamblers ($N = 7$), Hollander et al. (41) found that during a gambling task, monetary reward, as opposed to game points, was associated with significantly higher metabolic activity in the primary visual cortex (BA 17), cingulate gryus (BA 24), putamen, and OFC (BAs 47 and 10).

An understanding of the neurobiology of pathological gambling is beginning to emerge. Serotonin (5-HT) is linked to behavioral initiation and disinhibition, which are important in the onset of the gambling cycle and the difficulty in ceasing gambling behavior. Norepinephrine is associated with the arousal and risk taking in patients with pathological gambling. Dopamine is linked to positive and negative reward and the addictive component of pathological gambling (42). Studies suggest that potentially useful treatments for pathological gambling include the SSRIs clomipramine (43) and fluvoxamine (44–46), the opioid antagonist naltrexone (which may reduce the "high" associated with gambling) (47), the mood stabilizer lithium (48–50), and the AEDs carbamazepine (51), valproate (49), and topiramate (46).

While SSRIs may be effective for some patients with pathological gambling (43–46), those with comorbid conditions, like bipolar spectrum disorders, may relapse during such treatment. Thus treatment with AEDs for pathological gambling has been suggested, especially when bipolar mood symptoms are present. In the first controlled trial of mood stabilizers in pathological gambling, Pallanti et al. (49) compared the efficacy and safety of lithium and valproate in nonbipolar pathological gamblers. At the end of the 14-week trial, both the lithium and valproate groups showed comparable significant improvement in mean score on the Yale-Brown Obsessive-Compulsive Scale Modified for Pathological Gambling (YBOCS-PG). Thirteen (68.4%) of the nineteen patients taking valproate and 14 (60.9%) of the 23 patients taking lithium were responders based on a Clinical Global Impressions-Improvement Scale (CGI-I) score of much or very much improved.

Dannon et al. (46) compared the effectiveness of randomly assigned topiramate versus fluvoxamine in the treatment of male pathological gamblers. After 12 weeks, 9 of the 12 topiramate completers reported full remission of gambling behavior, and three completers had a partial remission. The CGI-I score was significantly better for the topiramate group at the 12-week visit as compared with baseline. Six of the eight fluvoxamine completers reported a full remission and the remaining two completers reported a partial remission. The fluvoxamine group showed improvement in the CGI-I score at week 12 but the change was not significant. Hollander (personal communication, 2007) recently Q4 completed a randomized, 14-week, double-blind, placebo-controlled, multicenter trial of topiramate (flexibly dosed to 300 mg or the maximum tolerated dose) in 50 subjects with pathological gambling. The primary endpoint was the change from baseline in the obsession component of the YBOCS-PG. Data analysis is presently ongoing.

Other ICDs

Topiramate has been reported to be effective in the treatment of a number of ICDs other than pathological gambling (46), including kleptomania (52), skin picking (53,54), trichtillomania (55), and IED (56,57). For example, topiramate augmentation of clomipramine/fluvoxamine was reported useful in a case of trichotillomania (58). In an open-label pilot study, Lochner et al. (55) evaluated topiramate monotherapy in 14 adults with trichotillomania. Patients received 16 weeks of flexible-dose treatment (50–250 mg/day), followed by a flexible-dose taper over two to four weeks. Severity of hair pulling in those who completed the 16-week trial ($N = 9$) decreased significantly from baseline to endpoint according to the Massachusetts General Hospital Hair Pulling Scale. Although CGI-I scores (a secondary outcome measure) suggested that hair pulling was not significantly reduced, six of nine completers were classified as responders. Five patients dropped out because of adverse effects. These results suggest that topiramate may be useful in the treatment of some patients with trichtillomania.

Prader-Willi syndrome (PWS) is a multisystem neurogenetic obesity disorder with behavioral manifestations, including hyperphagia, compulsive behaviors, mild to moderate mental retardation, and SIBs in the form of skin picking, nail biting, and rectal gouging. In the first published study of topiramate for the treatment of PWS or SIB, Shapira et al. (53) reported attenuation of SIBs resulting in lesion healing in three PWS adults treated with topiramate in an eight-week open-label trial. In another eight-week open-label study, Shapira et al. (54) evaluated adjunctive therapy with topiramate in eight adults with PWS. Topiramate did not significantly change compulsions, calories consumed, body mass index (BMI), or increased self-reported appetite. However, there was a clinically significant improvement in the self-injury characteristics (i.e., skin picking) of this syndrome. Double-blind or crossover studies are needed to establish the role of topiramate in attenuating SIB in PWS and other disorders involving SIB.

Regarding other ICDs, Dannon (52) reported three kleptomaniac patients who responded well to topiramate given either alone or in combination with SSRIs. Kaufman et al. (59) described two patients with ICDs with aggressive features and postencephalitic epilepsy where adjunctive tiagabine, a novel GABA reuptake inhibitor AED, was effective in the management of both epilepsy and severe impulsive and aggressive behaviors. This is consistent with observations that GABAergic modulation is important in impulsive aggression. De Dios Perrino et al. (56) reported three IED patients in whom good control of aggressive behavior was achieved using SSRIs in combination with carbamazepine. Indeed, in a survey completed by 2543 psychiatrists in the United States in 1988, carbamazepine was reported to be moderately to markedly effective in 65.2% of IED patients and 43.0% of BPD patients (57). In sum, AEDs may be effective treatments for ICDs, but more appropriately powered randomized, double-blind, placebo-controlled trials are needed.

ANTIEPILEPTIC DRUGS AND CLUSTER B PERSONALTY DISRODERS

Borderline Personality Disorder

We review here AED treatment studies across cluster B personality disorders. Since the majority of studies focus specifically on BPD, we will also discuss BPD in this section.

Personality disorders are characterized by interpersonal styles that are rigid and constant over time with onset before adulthood. BPD has been the most extensively studied among the current personality disorders. The DSM-IV-TR (34) classifies BPD as an axis II cluster B personality disorder with criteria that include affective instability, impulsive risk-taking behavior, inappropriate and intense anger, fear of abandonment, unstable relationships that rapidly shift between idealization and devaluation, unstable self-image, feelings of emptiness, dissociative experiences, SIB like superficial skin cutting or burning, and multiple suicide attempts. The designation of BPD as an axis II disorder reflects the historical conceptualization that personality disorders are psychologically and developmentally rooted, rather than biologically based and genetically determined like axis I disorders. Recently, alternative conceptualizations of BPD in particular and personality disorders in general have arisen, providing a theoretical rationale for the investigation into their neurobiology.

BPD is characterized by the core features of affective instability (possibly related to increased responsivity of the cholinergic system) and impulsivity and aggression (both thought to be related to reduced serotonergic brain activity). A typical symptom for BPD is the tendency to have outbursts of aggressive impulsivity (60). BPD is associated with high levels of functional impairment, treatment utilization, and mortality by suicide (61,62). Approximately 10% of patients with BPD commit suicide (63). BPD has an estimated prevalence of 1% to 2% of the U.S. population (34,64–67), with men constituting only about 25% of patients (67). The disorder accounts for approximately 10% of all psychiatric outpatients and 20% of acute inpatient hospitalizations (34,68,69). There are several psychotherapies for the treatment of BPD, like dialectic behavior therapy, but they are very time consuming, therapists must be specially trained, and patients must be highly motivated and many are resistant to treatment. Thus, Q6 pharmacotherapy may serve as a useful adjunct to psychotherapeutic interventions in BPD, and a combination of these approaches may be most effective (70,71).

In evaluating the use of medications for treating personality disorders, one can (*i*) treat the disorder itself, (*ii*) treat associated axis I disorders, or (*iii*) treat symptom clusters/psychobiological dimensions within and across disorders (72). Three symptom clusters that can be targeted in BPD are impulsivity and aggression, mood symptomatology, and psychotic-like symptoms. No single medication is thought to be effective for all three of these symptom clusters (73). New and old antipsychotics, monoamine oxidase inhibitors (MAOIs), SSRIs, and AEDs are all currently used for BPD (74). Tricyclics are used to decrease irritability and aggression, but are lethal in overdose; MAOIs are used for affective instability, but risks include hypertensive crisis; SSRIs are used to decrease anger, irritability, and aggression, but comorbid bipolar spectrum patients may develop rapid cycling; antipsychotics are used to improve psychosis, but side effects are common and controlled data are lacking; and benzodiazepines are used to decrease episodes of behavioral dyscontrol. In a review of the treatment of rapid-cycling bipolar disorder, which overlaps with BPD, Coryell (75) stated that placebo-controlled studies so far provided the most support for the use of lithium and lamotrigine as prophylactic agents. The combination of lithium and carbamazepine, valproate, or lamotrigine for maintenance has some support from controlled studies, as does the adjunctive use of olanzapine. However, it appears that AEDs are used more widely than lithium in treating BPD.

Valproate

Recently, AED trials have focused on valproate, a widely used mood stabilizer, and to a lesser extent on the newer anticonvulsants, for efficacy in BPD. Valproate has been shown to improve symptoms of irritability, agitation, aggression, and anxiety in patients with BPD (76–81). In an open-label study, eight BPD patients completed an eight-week trial of valproate (76). Half of the patients were rated as overall responders, with significant to modest decreases in depression, anxiety, anger, impulsivity, rejection sensitivity, and irritability, as measured by Overt Aggression Scale-Modified (OAS-M) and Symptom Checklist-90 (SCL-90) scores. Wilcox (77) treated 30 BPD inpatients in a naturalistic open study of valproate. Brief Psychiatric Rating Scale (BPRS) scores (particularly the anxiety subcomponents), aggressive outbursts, and time in seclusion significantly decreased during the six-week trial. In addition to treating the aggressive and impulsive symptoms of BPD patients, valproate may also be helpful in treating BPD patients who report changeable mood (i.e., those who have mood instability but who are subsyndromal for major depression or hypomania) (82). In one valproate treatment study, six of nine BPD patients with mood instability (defined by the BPD DSM-III-R diagnostic criterion "affective instability due to marked reactivity of mood"), without bipolar or current major depression, were responders in that their CGI score on their last visit was "much improved" or better (82). Responders showed a greater reduction in Hamilton Rating Scale for Depression (HAM-D) scores than nonresponders.

In a preliminary, double-blind trial, BPD outpatients were treated for 10 weeks with valproate ($N = 12$) or placebo ($N = 4$) (80). There was significant improvement from baseline in measures of global symptom severity (as assessed by the CGI-I) and functioning [as assessed by the Global Assessment of Function (GAF) scale], following treatment. A high dropout rate precluded finding significant differences between the treatment groups in the intent-to-treat (ITT) analyses. However, all results were in the predicted direction so that patients in the treatment group had decreases in scores on the Aggression Questionnaire and the Beck Depression Inventory (BDI) compared with placebo. In another controlled, double-blind study of valproate, efficacy was examined in 30 women with comorbid BPD and bipolar II disorder over six months of treatment (81). Valproate, at an average dose of 850 mg/day (blood levels between 50 and 100 mg/L), was well tolerated and superior to placebo in diminishing interpersonal sensitivity and anger/hostility as measured by the SCL-90 and overall aggression as measured by the OAS-M. Taken together, these studies suggest valproate may be more effective than placebo for global symptomatology, level of functioning, aggression, and depression in BPD.

Since valproate may improve impulsive aggression, irritability, and global severity in patients with cluster B personality disorders (9), Hollander et al. (83) examined clinical characteristics of BPD outpatients that might predict response of impulsive aggression to valproate. In this randomized, double-blind, 12-week study, valproate ($N = 20$) was superior to placebo ($N = 32$) in reducing impulsive aggression in BPD patients. Both pretreatment trait impulsivity and state aggression symptoms, independently of one another, predicted a favorable response to valproate relative to placebo. However, baseline affective instability did not affect differential treatment response. These may help identify BPD patient subgroups or baseline characteristics (e.g., those with high levels of trait impulsivity or state aggression) that could guide future trials of AEDs. These data also suggest that BPD may be characterized by independent symptom domains that are amenable to treatment (40,84).

Carbamazepine and Oxcarbazepine

Carbamazepine, an anticonvulsant with effects on subcortical limbic structures, is effective in the treatment of several psychiatric disorders, including bipolar mania. Because patients with BPD show prominent affective symptomatology and symptoms suggestive of an epileptoid disorder, carbamazepine might be useful in treating BPD. In fact, in a double-blind, crossover trial, carbamazepine decreased the severity of behavioral dyscontrol in 11 women with BPD significantly more than placebo (85). In another double-blind, placebo-controlled, crossover study, carbamazepine led to a dramatic, highly significant decrease in clinician-rated behavioral dyscontrol and had a modest effect on mood in female BPD outpatients with prominent behavioral dyscontrol and without current major depression (86). However, one carbamazepine study of 20 BPD inpatients without concurrent depression or concomitant medications yielded negative results (87). After four weeks of treatment at standard doses, carbamazepine was no better than placebo in treating depression, behavioral dyscontrol, or global symptomatology. In another study, 3 (18%) of 17 BPD patients developed melancholia during carbamazepine treatment, which remitted upon discontinuation of carbamazepine (88). Thus, while carbamazepine may be an effective medication for some BPD patients, clinicians should be alert for any worsening in depressive symptoms.

More recently, Bellino et al. (89) tested 17 DSM-IV-TR-diagnosed BPD outpatients with oxcarbazepine, an AED that is structurally related to carbamazepine and sometimes used for treating patients with bipolar disorders, substance abuse, schizoaffective disorder, and treatment-resistant psychosis. Patients were administered oxcarbazepine 1200 to 1500 mg/day and evaluated at baseline, and after 4 and 12 weeks of treatment. A statistically significant response to oxcarbazepine was observed according to change in mean scores on the CGI-S, BPRS, and Hamilton Rating Scale for Anxiety (HAM-A); in interpersonal relationships, impulsivity, affective instability, and outbursts of anger items; and in total score of the Borderline Personality Disorder Severity Index. Oxcarbazepine was well tolerated with no severe adverse effects; four patients discontinued treatment due to noncompliance. Thus, oxcarbazepine may be an effective and safe treatment for some BPD patients. However, controlled studies are needed.

Topiramate

In an eight-week, double-blind, placebo-controlled trial of topiramate to treat aggression in females with DSM-IV-diagnosed BPD, the topiramate group ($N = 19$) showed significantly more efficacy than the placebo group ($N = 10$) (90) as measured by four subscales (i.e., the state-anger, trait-anger, anger-out, and anger-control subscales) of the State Trate Anger Expression Inventory (STAXI) scale. Significant changes on the same four STAXI subscales were also observed in males with DSM-IV-diagnosed BPD treated with topiramate ($N = 22$) in a similarly designed eight-week, double-blind, placebo ($N = 20$) controlled study (91). In both studies, topiramate was well tolerated and significant weight loss was observed. These findings suggest topiramate may be a safe and effective treatment of anger in both men and women with BPD and correspond with other studies where topiramate therapy resulted in significantly decreased symptoms of aggression (92,93).

Recently, Loew et al. explored whether topiramate could influence BPD patients' borderline psychopathology, health-related quality of life, and interpersonal problems (94,95). DSM-IV SCID-II–diagnosed BPD women were randomly

assigned in a 1:1 ratio to topiramate titrated from 25 to 200 mg/day ($N = 28$) or placebo ($N = 28$) for 10 weeks. Significant changes were observed on the somatization, interpersonal sensitivity, anxiety, hostility, phobic anxiety, and Global Severity Index scales of the SCL-90 in the topiramate-treated subjects after 10 weeks. In addition, significant differences were found on all eight scales of the SF-36 Health Survey and in the overly autocratic, competitive, introverted, and expressive scales of the Inventory of Interpersonal Problems. Significant weight loss was also observed.

Finally, do Prado-Lima et al. (96) reported a woman with BPD and a history of childhood trauma who showed a significant clinical response with a low dosage of topiramate. The authors suggested that topiramate might decrease emotional and behavioral reactivity by facilitating memory extinction.

Lamotrigine

In a small, open trial of lamotrigine in eight BPD patients without concurrent major depression, two subjects discontinued because of adverse events or noncompliance and three did not respond (97). However, the remaining three were robust responders with a marked increase in their overall level of functioning, a cessation of impulsive behaviors like promiscuity, substance abuse, and suicidality, and maintenance of response at one-year follow-up. In a retrospective study of borderline symptoms in bipolar patients, it was estimated that 43% of this subgroup experienced a reduction in such symptoms during lamotrigine treatment (98).

Tritt et al. (99) investigated the efficacy of lamotrigine in the treatment of aggression in 24 women meeting Structured Clinical Interview for DSM-IV (SCID) criteria for BPD. In this double-blind, placebo-controlled study, subjects were randomly assigned in a 2:1 ratio to lamotrigine ($N = 18$) or placebo ($N = 9$) for eight weeks. Compared with the placebo group, highly significant changes on four STAXI scales (e.g., state-anger, trait-anger, anger-out, anger-control) were observed in subjects treated with lamotrigine after eight weeks. All the patients tolerated lamotrigine relatively well, and it had no clinically significant effect on body weight.

Weinstein and Jamison (100) assessed lamotrigine treatment for affective instability symptoms of BPD patients. Charts of patients treated with lamotrigine in a private practice during 2003–2004 were reviewed. Patients were included in the analysis if they had been given a DSM-IV-R diagnosis of BPD; had continued to display affective instability while taking their previous medications before lamotrigine initiation; had received a CGI-S score before and after lamotrigine therapy; had been treated with lamotrigine, as monotherapy or adjunctive therapy, at a dose ranging from 50 to 200 mg/day; and continued to take lamotrigine for at least three months. The charts of 13 patients met inclusion criteria. All patients were female, 19 to 43 years of age, and had reported continuing symptoms of affective instability despite treatment with two to seven psychotropic drugs, including, but not limited to, fluoxetine, paroxetine, escitalopram, buproprion, and clonazepan. The duration of lamotrigine treatment ranged from 3 to 15 months. The patients had initial CGI-S scores of 5 or 6 and final scores of 1 or 2, except one patient with an initial score of 3 and a final score of 1 and another patient with an initial score of 6 and a final score of 7.

In sum, there is preliminary evidence that lamotrigine may have efficacy in treating BPD symptomatology, especially symptoms of anger, affective instability, and impulsivity.

Cluster B Personality Disorders

Many researchers have recommended AEDs for the treatment of the affective, impulsive, and aggressive symptoms of cluster B personality disorders in general. Stein (101) has suggested that carbamazepine and lithium may help some personality-disordered people with episodic behavioral dyscontrol and aggression, even in the absence of affective, organic, or epileptic features. Stone (63) has suggested that BPD patients with bipolar II may benefit from lithium or from carbamazepine if irritability is prominent. In a review of double-blind, placebo-controlled drug trials for personality disorders, Hori (102) concluded that patients with BPD and behavioral dyscontrol respond to carbamazepine, which reduces episodes of dyscontrol, and that patients with personality disorders with aggressive behavior respond to lithium. Coccaro and Kavoussi (103) concluded that affective instability in BPD, which may be related to abnormalities in the brain's adrenergic and cholinergic systems, appears to respond to lithium and carbamazepine. In another review, Pelissolo and Lepine (104) argued that for cluster B personality disorders, especially antisocial and BPD, positive results have been obtained using lithium, carbamazepine, and valproate for aggressive and impulsive behaviors.

In an eight-week open trial of valproate in patients with at least one personality disorder who had failed one SSRI trial, six of eight completers showed a significant decline in irritability and impulsive aggression on the OAS-M score (78). Hollander et al. (9) conducted a large, placebo-controlled, multicenter trial of valproate for the treatment of impulsive aggression in cluster B personality disorders, IED, or posttraumatic stress disorder (PTSD). These different diagnoses were included in the same study, as they have the symptom dimension of impulsivity and aggression, which could benefit from the same treatment. Entry criteria required evidence of current impulsive-aggressive behavior (e.g., two or more impulsive-aggressive outbursts per week on average for the previous month) and an OAS-M score of 15 or greater. Ninety-one (43 valproate; 48 placebo) of the 96 randomized cluster B personality disorder patients were included in the ITT data set (defined as subjects who received at least one dose of the study drug and had at least one postbaseline OAS-M rating). The most common primary diagnosis was BPD (55% of patients), followed by cluster B personality disorder NOS (21%), narcissistic (13%), antisocial (10%), and histrionic (1%) personality disorders. Subjects were randomized to 12 weeks of valproate or placebo, and OAS-M (aggression and irritability) and CGI scores were obtained weekly (except for weeks 5 and 7).

A treatment effect was not observed when all three diagnostic groups were combined, but valproate was superior to placebo in the treatment of impulsive aggression, irritability, and global severity in the subgroup of patients with cluster B personality disorders. A treatment effect was observed in both ITT and evaluable (defined as receiving at least 21 days of treatment with study drug) data sets for cluster B personality disorder patients in terms of average OAS-M Aggression scores over the last four weeks of treatment. In the cluster B evaluable data set, statistically significant treatment differences favoring valproate were also observed for component items of the OAS-M Aggression scale (including verbal assault and assault against objects), OAS-M Irritability scale, and CGI-S at multiple time points throughout the study. Across psychiatric diagnoses, 21 (17%) patients in the valproate group prematurely discontinued because of an adverse event, compared with four (3%) patients in the placebo group.

These results support previous findings of decreased impulsive-aggressive behavior and irritability in BPD patients treated with valproate (80), including in those who failed to respond to other agents with antiaggressive properties (i.e., SSRIs) (78). Unlike a previous pilot study where valproate was superior to placebo for the treatment of irritability and hostility in women with bipolar II and BPD (81), patients in the study by Hollander et al. (9) were excluded if they had bipolar disorder I or II with recent (i.e., past year) hypomania. This suggests that the effect of valproate in impulsive aggression may be unrelated to its effect in mania. However, the possibility that the impulsive aggression of cluster B personality disorders has an affective component or that valproate is treating a subclinical mood disorder in cluster B personality disorders cannot be excluded.

Gabapentin is an AED structurally similar to GABA, with unclear mechanisms of action and a good safety profile. Biancosino et al. (105) reported a case of successful gabapentin treatment of chronic impulsive-aggressive behavior in a patient with severe BPD. Morana et al. (106) treated 29 cluster B personality disorder outpatients (8 antisocial, 13 impulsive, 7 histrionic, and 1 narcissistic type) with gabapentin (1200 mg/day), alone or with other drugs (antipsychotics, mood stabilizers, and benzodiazepines). After six weeks of treatment, there was an improvement in 23 (79.9%) patients, with a decrease in aggressiveness, impulsivity, antisocial behavior, and drug abuse and an improvement in their concentration, introspection capabilities, and interest in productive activities, as reported by patients and their caregivers. Morana and Camara (107) found that after more than four years of study of personality disorder patients from the Personality Disorder Ambulatory of the Department of Psychiatry of Sao Paulo University Medical School, about 79.3% of the patients treated with gabapentin had reduced their antisocial behaviors, as reported by patient informers. The authors observed a decrease in aggressiveness, impulsiveness, offender behavior, and drug abuse, and a general improvement in tolerance, concentration, and introspective capacity, with a greater interest in productive activities. It has been suggested that gabapentin reduces reactivity and turbulent behavior perhaps because of its inhibitory effect in central neurotransmission (108). The authors concluded that, in their clinical experience, gabapentin was the most effective mood stabilizer for the treatment of personality disorders.

Summary

A symptom-specific method using current empirical evidence for drug efficacy in each symptom domain of BPD is proposed for treatment. Drugs in each medication class have some potential utility against specific symptoms of BPD (109). As there is no "drug of choice" to treat BPD, a more rational clinical approach might be to treat different symptom clusters (e.g., cognitive, affective, impulsive, and aggressive) rather than the disorder itself. On the basis of the above evidence, we suggest that selective AEDs may be effective in treating the affective, impulsive, and aggressive symptoms of BPD and other cluster B personality disorders.

ANTIEPILEPTIC DRUGS AND IMPULSIVITY AND AGGRESSION ACROSS DIAGNOSES

The antiaggressive effects of AEDs in patients with neurological disorders make them good candidates for the treatment of aggression in the context of psychopathology. AEDs are generally considered the treatment of choice for patients with

abnormal EEG findings and outbursts of rage (110). In a retrospective chart review, Salpekar et al. (111) identified 38 children with bipolar spectrum disorders and epilepsy comorbidity. Common bipolar symptoms included impulsivity, psychomotor agitation, and explosive rage. Forty-two medication trials with 11 different AEDs were identified. Of the 30 cases in which AED monotherapy was attempted, carbamazepine, valproate, lamotrigine, and oxcarbazepine were associated with better CGI-I ratings than were other AEDs. In many cases, selected AEDs appeared to simultaneously treat both epilepsy and mood disorder. However, with the exception of cluster B personality disorders, AEDs have received only preliminary exploration in the treatment of impulse control and aggression in psychiatric disorders, without an associated seizure disorder.

Nonetheless, there is some evidence for the efficacy of valproate and carbamazepine for the treatment of pathological aggression in patients with organic brain syndromes, dementia, psychosis, and, as discussed, personality disorders (109,110). Firm evidence for the efficacy of valproate or carbamazepine in managing aggression and/or agitation following traumatic brain injury (TBI) is lacking (112). In a literature review of AEDs for migraine, neuropathic pain, movement disorders, pervasive developmental disorders, bipolar disorder, and aggressive behavior in children and adolescents, Golden et al. (113) concluded that valproate is "probably effective" in decreasing aggressive behavior, carbamazepine is "probably ineffective" in treating aggression, and lamotrigine is "possibly ineffective" for the core symptoms of pervasive developmental disorders. They also concluded that the data are insufficient to make recommendations about the efficacy of AEDs in these conditions in children and adolescents. Q10

The likelihood of aggression may increase from stress or environmental overstimulation, problems related to impulsivity, or neurotransmitter balances, favoring dopamine and excitatory amino acid transmission over serotonin and inhibitory amino acid (GABA) transmission (114). AEDs may work by altering the inhibitory excitatory amino acid balance in favor of GABA, thereby protecting against overstimulation and raising the convulsive threshold when aggression is associated with a seizure disorder. Useful AEDs might also be those that combine dopaminergic and serotonergic actions (114).

Treatments for aggression should be based on the underlying causes. Barratt (115) proposed that aggression could be divided into three general categories: (*i*) medically related, where aggression is a symptom secondary to a neurological, psychiatric, or other medical disorder; (*ii*) premeditated, predatory, or planned, where the aggressive behavior is an instrumental response; and (*iii*) impulsive, where aggression is a trigger response in that information is not processed in an adaptive way during the temper outburst. Barratt hypothesized that certain anticonvulsants (e.g., phenytoin, carbamazepine) would be effective for treating impulsive aggression.

Valproate

Valproate, which enhances GABA neurotransmission, was first introduced as an AED in 1967. Its use in the treatment of aggressive and violent behaviors has been reported in the literature as far back as 1988. This literature, which includes several double-blind, placebo-controlled studies (9,80,81,83,116), supports the use of valproate in the treatment of hostility/aggression, impulsive aggression, and affective instability in patients in a variety of psychiatric and neuropsychiatric disorders.

Thus, valproate has been reported to be effective against impulsive aggression and/or hostility in subjects with bipolar disorder (9,74,77,80–83,117) and adolescents with aggression and labile mood (118,119). Improved behavioral dyscontrol and aggression with valproate treatment has also been noted in patients with PTSD (120–122), temper outbursts (118,119,123), TBI (124,125), dementia (116,126–129), and autism (130).

In a review of studies of nonbipolar subjects with aggressive and violent behaviors (the most frequent diagnoses were dementia, organic brain syndromes, and mental retardation), valproate was found to be effective in 77% of 164 subjects in 17 studies, though these were open studies that often included more than one treatment (131). Wroblewski et al. (125) described the effectiveness of VPA in reducing and improving destructive and aggressive behaviors in five patients with TBI. In all cases, valproate was effective after other pharmacological interventions had failed, and neurobehavioral improvement was fairly rapid, often within one to two weeks. Although AEDs may be best suited for subacute or chronic treatment (114), rapid stabilization of severe agitation has been reported with intravenous valproate (132). Buchalter and Lantz (127) described a patient with vascular dementia in whom valproate led to reduced overt aggression, diminished impulsivity, and improved functional status. In a retrospective study of a long-term care database of elderly nursing home residents with a history of dementia-related behavior problems, Meinhold et al. (133) found that valproate therapy had beneficial effects on various behavioral, mood, and cognitive indicators, as monotherapy with benzodiazepines, and with antipsychotics, and at both higher and lower doses. In general, the higher-dose valproate group had more favorable results.

In a retrospective study (130), 14 patients with DSM-IV-diagnosed autism, Asperger's disorder, or pervasive developmental disorder NOS, with or without a history of seizure disorders or EEG abnormalities, received open-label treatment with valproate. Ten (71%) patients had a sustained response to valproate, as assessed by the CGI-I scale. Improvement was noted in the core autistic symptoms of social interaction, speech/communication skills, and repetitive behaviors as well as the associated features of affective instability, impulsivity, and aggression. Valproate was generally well tolerated. By contrast, no treatment difference was observed between groups in a prospective, eight-week, randomized, double-blind, placebo-controlled study of 30 outpatient subjects ($N = 20$ boys) with pervasive developmental disorders (ages 6–20 years) with significant aggression (134). However, these negative findings should not be considered conclusive, partly because of the large placebo response, subject heterogeneity, and small sample size.

Evidence supporting the use of valproate in the treatment of juvenile bipolar disorder with reactive aggression has grown (135,136). In one study, three boys with ADHD associated with giant somatosensory evoked potentials (SEP) responded well to valproate extended-release (ER) in particular, showing reduced hyperactivity and impulsivity (137). In two patients, previous methylphenidate treatment had worsened symptoms, suggesting that they may have had bipolar spectrum conditions. Valproate was also effective in a randomized, controlled trial of adolescent males with conduct disorder openly treated with high-dose or low-dose VPA (138). There was significant improvement in the high-dose group on a number of outcome measures, including self-reported weekly impulse control. Donovan et al. (119) sought to replicate open-label findings where 10 adolescents with a disruptive behavior disorder, who met operationalized criteria for explosive temper and mood lability, showed improvement with valproate for five weeks (118).

In the double-blind, placebo-controlled crossover study (119,20), outpatient children and adolescents (ages 10–18 years) with a disruptive behavior disorder (oppositional defiant disorder or conduct disorder), who met the specific criteria for explosive temper and mood lability, were randomly assigned to receive six weeks of valproate or placebo. At the end of phase one, 8 of 10 subjects responded to valproate and 0 of 10 responded to placebo. Twelve of the 15 subjects who completed both phases had a superior response to valproate.

In a randomized, double-blind, 28-day study, valproate and quetiapine showed similar efficacy for the treatment of impulsivity and reactive aggression related to co-occurring bipolar and disruptive behavior disorders in adolescents ($N = 33$) (139). In a retrospective, case-controlled study, Gobbi et al. (140) compared the effects of topiramate, valproate, and their combination in 45 psychiatric inpatients with schizophrenia, schizoaffective, or bipolar disorder with marked aggression and agitation. Topiramate-treated patients showed a decrease in mean OAS scores, episodes of agitation, and strict surveillance interventions. The effect was similar in the valproate-alone and combination valproate-topiramate treatment groups. However, valproate alone, but not topiramate alone, decreased the intensity of agitation episodes; and valproate alone and the valproate-topiramate combination decreased the number of psychotic disorganization episodes. MacMillan et al. (141) reviewed medical records of 31 pediatric bipolar disorder patients (age < 18 years) with severe aggression who received valproate ($N = 20$) or oxcarbazepine ($N = 11$). Overall CGI-S scores and CGI-S scores specific to aggression significantly improved from baseline to the four-month time point with valproate but not oxcarbazepine. Discontinuation rates from adverse events were similar. However, more discontinuations due to worsening aggression occurred with oxcarbazepine (27.3% vs. none for valproate). In a medical records review of 42 patients (ages 12–19 years) hospitalized for acute mania and discharged with a diagnosis of DSM-III-R or DSM-IV bipolar disorder, a history of ADHD was associated with a significantly diminished acute response to both valproate and lithium as a treatment for their bipolar manic phase (142). Response rates for lithium versus valproate in subjects with and without ADHD did not differ.

Barzman et al. (143) retrospectively reviewed the charts of 46 children and adolescents admitted to a crisis stabilization center with prominent impulsive aggression and irritability who met criteria for a potential pediatric bipolar phenotype and who responded to valproate. Significant improvements were obtained on the Children's Global Assessment Scale, with significant decreases on the OAS and the Anger-Hostility Subscale of the SCL-90 at discharge, following a maximal 14-day stay. No severe side effects were reported. The above data are in line with valproate response in children and adolescents with explosive temper and mood instability (118,119) and suggest that such symptoms, together with impulsive aggression, irritability, and other manic symptoms, may constitute a pediatric valproate-responsive bipolar spectrum disorder. In a 12-week, open-label trial of valproate in 24 bipolar offspring, ages 6 to 18 years (17 boys), with mixed diagnoses of major depression, cyclothymia, ADHD, and oppositional defiant disorder, 71% of subjects were considered valproate responders by the OAS (144). Thus, youths who were at high risk for bipolar disorder experienced an overall decrease in aggressive behavior in response to valproate.

Prospective, randomized, double-blind, placebo-controlled trials are needed to further assess valproate's optimal usage for the treatment of aggression and impulsivity across psychiatric disorders.

Carbamazepine and Oxcarbazepine

In the 1980s, carbamazepine became an AED of primary interest in treating impulsive aggression because it was the drug of choice for treating temporal lobe epilepsy patients with aggressive outbursts and irritability (145). Several reviews have since then concluded that carbamazepine reduces aggressive and associated behaviors across a wide range of diagnoses (146–149). Carbamazepine has been reported effective in treating pathological aggression in dementia (150) and in decreasing combativeness, agitated behavior, irritability, and disinhibition in subjects with head injuries (151,152). Freymann et al. (153) described the successful use of carbamazepine in a 78-year-old Alzheimer's disease patient with hypersexual behavior. The efficacy of carbamazepine in this case is in parallel to its effects on aggression and agitation in dementia (150). One open-label study of inpatient children with conduct disorder found statistically and clinically significant declines of explosiveness and aggression (154). A double-blind, placebo-controlled trial, however, found no difference between carbamazepine and placebo, and side effects were common (146). Indeed, the few placebo-controlled trials with carbamazepine have been small and in diverse patient populations (147,148). For example, Mattes (155) randomly assigned propranolol or carbamazepine treatment for temper outbursts to 80 patients with diverse diagnoses. Both medications were beneficial, but a diagnosis of ADHD predicted better response to propranolol, and a diagnosis of IED predicted better response to carbamazepine.

The ICD-10 diagnosis "Organic Personality Disorder," listed under "Personality Change Due to a General Medical Condition" in the DSM-IV, may involve aggression and impulsivity. Many different treatments have been proposed for this condition, including carbamazepine. Munoz and Gonzalez Torres (156) described a 28-year-old male who had aggressive episodes along with an intensification of previous personality traits, sexual exhibitionism, promiscuity, suspiciousness, and low impulse control after a severe brain injury sustained in a car accident. Antipsychotics, benzodiazepines, and antidepressants had no effect. After two months of carbamazepine treatment, the patient had marked improvement with the absence of aggressive episodes and exhibitionistic behavior, a tendency toward normalization of mood and anxiety, stabilization of his social and family relationships, and employment. Morikawa et al. (157) reported a 19-year-old male who had a personality change, marked by irritability, aggression, labile mood, childishness, irresponsibility, and lack of motivation, six months after a mild injury to his left frontotemporal cortex from a motorbike accident. He was diagnosed with posttraumatic personality disorder and treated with clonazepam, which moderately improved his symptoms but caused drowsiness. Within a few days of the addition of carbamazepine, he improved to his preinjury personality. After clonazepam was discontinued, he maintained good mental status and at two-year follow-up continued to be well. Lewin and Sumners (158) described an 18-year-old man who, following a traffic accident, developed episodic dyscontrol. Two years post injury, carbamazepine treatment was started and his aggressive outbursts subsided.

Oxcarbazepine, like carbamazepine, is effective for complex partial seizures and may have mood-stabilizing effects (159). In a double-blind, placebo-controlled, 10-week study, adult outpatients with clinically significant impulsive aggression were randomized to placebo ($N = 24$) or oxcarbazepine ($N = 24$) (160). Nine patients dropped out because of adverse events, but 45 completed at least four weeks of treatment. Results showed a benefit from oxcarbazepine compared with

placebo on OAS-M scores and patient-rated global improvement. Guadino et al. (161) described an adolescent with treatment-resistant aggression (and a mood disorder and ADHD), which improved with oxcarbazepine, the only side effect being sedation. Cordas et al. (162) presented two cases of severe bulimia and BPD, in which self-mutilating behavior was successfully controlled with oxcarbazepine treatment.

Topiramate

Topiramate, a newer AED, which acts on voltage-activated sodium channels and glutamate and GABA receptors, has also been reported to be effective in a variety of aggressive patients (92). In a retrospective chart review study, Janowsky et al. (93) examined topiramate treatment in 22 severely or profoundly intellectually disabled, institutionalized adults, most with a concurrent mood disorder. Patients were treated for aggression, SIBs, destructive/disruptive behaviors, and/or other challenging and maladaptive behaviors. Significant decreases in global severity scores, cumulative aggression, and worst behavior rates occurred, especially when comparing the three months before and the three to six months after starting topiramate. In a randomized, double-blind, placebo-controlled, 10-week study of topiramate in 64 females diagnosed with recurrent major depressive disorder, topiramate significantly reduced anger and depressive symptoms compared with placebo (163). There was also significant weight loss in the topiramate group and topiramate was relatively well tolerated. In seven patients with PWS, topiramate reduced aggressive and SIB, improved mood, and stabilized weight (164). These reports correspond with other studies in which topiramate resulted in significantly decreased aggressive symptoms (90,91).

Impulsivity plays a significant role in a wide range of psychiatric disorders including eating disorders like BED. Topiramate has also shown efficacy in the treatment of a number of disorders involving impulsivity including BED (165,166). BED is characterized by recurrent episodes of binge eating that are not followed by the regular use of inappropriate compensatory weight loss behaviors. It is often associated with overweight or obesity and psychopathology. The literature offers support, including from double-blind, placebo-controlled trials, for the use of antidepressants, appetite suppressants (e.g., sibutramine), and AEDs in the treatment of BED (167–169). Topiramate, in particular, appears to be promising for the treatment of BED because of its beneficial effects on body weight as well as impulsivity.

In a preliminary naturalistic, open-label study with topiramate, 9 of 13 BED outpatients showed a moderate or better response of binge eating symptoms after beginning treatment that was maintained for 3 to 30 months (165). Two other patients had moderate or marked responses that subsequently diminished and the remaining two patients had a mild or no response. In another preliminary study, treatment with topiramate (150 mg daily) was administered over 16 weeks to eight obese patients with BED and no medical or psychiatric comorbidity (170). All six of the trial completers showed reduced binge eating. Four patients had a complete remission, and two had a marked reduction in binge eating frequency. Patients also had significant weight loss. In a 14-week, double-blind, flexible-dose topiramate trial, 61 BED outpatients with obesity were randomly assigned to receive topiramate ($N = 30$) or placebo ($N = 31$) (166). Compared with placebo, topiramate resulted in a significantly greater rate of reduction in binge frequency, binge day

frequency, BMI, weight, and scores on the CGI-S and the Y-BOCS modified for binge eating (Y-BOCS-BE) (166). Topiramate was also found to have positive effects for the long-term treatment of BED in a 42-week, open-label extension trial (171) of the acute study (166). For all patients ($N = 43$) receiving topiramate during either the double-blind or open-label extension study, there was a significant decline from baseline to final visit in weekly binge frequency, CGI-Score, Y-BOCS-BE total, and compulsion, and obsession subscale scores, weight, and BMI.

Zilberstein et al. (172) analyzed 16 patients with binge eating and inadequate weight loss after adjustable gastric banding while receiving topiramate for three months (12.5–50 mg/day). There was a mean increase in excess weight loss from 20.4% to 34.1% without the need for band readjustment. Two patients, however, could not tolerate topiramate. Dolberg et al. (173) reported the effects of adjunctive topiramate on eating patterns and weight in 17 patients with TBI, posttraumatic epilepsy, and weight gain of various etiologies. The six patients with BED had the most pronounced effects, with marked decreases in binges and a normalization of BMI. In another study, three obese BED patients, who had recurrent binge eating and weight gain after initially successful bariatric surgery, reported complete improvement of their binge eating and displayed weight loss after receiving topiramate for 10 months on average (174). De Bernardi et al. (175) reported a BED patient who was unresponsive to several treatments but was successfully treated with topiramate. In a 10-week double-blind, placebo-controlled study, topiramate was also effective in reducing the frequency of binging/purging and body weight in bulimic patients (176).

Topiramate may also be effective in treating self-mutilating behavior. Topiramate improved self-mutilation and manic symptoms in two patients with bipolar disorder and BPD (177). Further, topiramate (200 mg/day) administered in an on-off-on design to a 24-year-old woman with bipolar II depression and BPD led to long-term remission of self-mutilation despite the persistence of depression (178). No self-injurious acts occurred over nine months, and mood was sufficiently stabilized.

Dolengevich et al. (179) evaluated 11 child and adolescent outpatients with impulsive behavioral disorders by DSM-IV criteria at one and three months after starting topiramate treatment. There were significant differences in the cognitive impulsivity subscale and total score of the Barratt Impulsivity scale after one month and the motor impulsivity subscale after three months. Thus, topiramate may be an effective treatment for impulsivity in children and adolescents as well as in adults with some psychiatric disorders. More studies with larger samples and control groups are needed to confirm the efficacy of topiramate for the treatment of aggression and impulsivity in all age groups.

Levetiracetam

There is preliminary evidence that levetiracetam, FDA approved as an adjunctive treatment for partial-complex seizures, may be effective in some psychiatric disorders characterized by affective lability, impulsivity, and anxiety (180–183). In an open-label prospective study of 10 autistic boys aged 4 to 10 years, levetiracetam significantly reduced hyperactivity, impulsivity, mood instability, and disruptive outbursts (180). Aggressive behavior showed significant improvement only in subjects who were not recently weaned from medications that reduced aggression (e.g., risperidone, carbamazepine, desipramine). However, in a 10-week, double-blind,

placebo-controlled trial of levetiracetam in 20 autistic children aged 5 to 17 years, no significant difference was found between drug and placebo groups in terms of change in CGI-I, Aberrant Behavior Checklist, Children's Y-BOCS, or Conners' scales (184). These findings suggest that levetiracetam may not improve the behavioral disturbances of autism, but are limited by the small sample size and lack of stratification of the autistic sample at baseline.

In some studies, levetiracetam has actually increased aggression as a side effect. Dinkelacker et al. (185) reported 33 patients with long-standing histories of epilepsy who experienced aggressive episodes during levetiracetam therapy (3.5% of levetiracetam-treated patients vs. <1% of patients not receiving levetiracetam). Among these cases, 24 showed only moderate, transient irritability, with 10 patients requiring reduction or discontinuation of levetiracetam; but nine patients had severe aggressive symptoms with physical violence, two of whom needed psychiatric emergency treatment. Weber et al. (186) gave levetiracetam to 10 generalized epilepsy patients, and one patient with Lennox-Gastaut syndrome discontinued the drug because of aggression. In an observational survey, 128 (44.9%) of 285 pediatric patients (mean age 9.9 years) with refractory generalized and focal epilepsy reported mild to moderate side effects after receiving levetiracetam as an add-on open-label treatment (187). Behavioral changes were the second most frequent side effect after somnolence, included aggressive behavior in 44 patients (15.4%) and prompted discontinuation of the drug in 23 cases (8.1%). The most common behavioral adverse event was aggression, which was seen in 30 patients (10.5%) and was often severe. Two patients violently attacked others, which they had never done before. In another study (188), 11 (13%) of 85 pediatric patients (mean age 10.5 years) with refractory generalized and focal epilepsy, who received levetiracetam as add-on treatment, reported mild to moderate side effects, consisting most frequently of general behavioral changes, aggression, and sleep disturbances, which ceased after decreasing the levetiracetam dosage.

In sum, levetiracetam may reduce impulsivity, mood instability, and aggression in some populations, but studies in other patient populations, including BPD, are warranted. Morever, because of reports of increased aggression, the behavioral tolerability of levetiracetam should be monitored carefully, especially in patients with histories of aggression.

Gabapentin

Gabapentin increases CNS GABA, a neurotransmitter important for the control of aggressive behavior and has been reported to have antiaggressive effects across several disorders (189). Thus, several studies have reported significant improvement with gabapentin of aggressive behavior in dementia patients (190,191). In a retrospective chart review, Hawkins et al. (192) examined the use of gabapentin for the treatment of aggressive and agitated behaviors in 24 nursing home patients with DSM-IV-diagnosed dementia. On the CGR-I, 17 of 22 patients were rated as much or greatly improved, four were minimally improved, and one remained unchanged. Two patients discontinued the medication because of excessive sedation. No other significant side effects were noted after treatment for up to two years. Alkhalil et al. (193) described three dementia nursing home residents whose sexual disinhibition was effectively treated with gabapentin.

McManaman and Tan (194) described a patient with Lesch-Nyhan syndrome (an X-linked disorder of purine metabolism) whose SIB was effectively treated with

gabapentin. Gupta et al. (195) described a patient with aggression and violent behavior due to DSM-IV-diagnosed conduct disorder whose symptoms were controlled with gabapentin after he failed a trial of valproate. In another case (196), gabapentin treatment resulted in a decrease in the frequency and intensity of violent episodes in a young patient with IED, ADHD, organic mood disorder secondary to a TBI, and a simple partial seizure disorder. Cherek et al. (189) measured aggression in 20 adult parolees with a pattern of antisocial behavior ($N = 2$ females), using the Point Subtraction Aggression Paradigm, which provided subjects aggressive, escape, and monetary reinforced response options. Ten subjects had a history of conduct disorder (CD^+) and 10 had no history of conduct disorder (non-CD). Acute doses (200, 400, and 800 mg) of gabapentin had similar effects on aggressive responses among both CD^+ and non-CD control subjects. Aggressive responses of CD^+ and non-CD subjects increased at lower gabapentin doses and decreased at the highest dose (800 mg). Specifically, gabapentin increased escape responses for both groups at the lowest dose, but then produced dose-related decreases at the two higher doses in both groups. No changes in monetary reinforced responses were observed, suggesting an absence of CNS stimulation or sedation.

Phenytoin

Although phenytoin did not improve aggressive behavior in children with temper tantrums in one early study (197), it has been reported to reduce the frequency of impulsive-aggressive behavior in a variety of conditions (115,198), to alter mid-latency-evoked potentials (199), and to significantly reduce violent outbursts in psychiatric patients with episodic dyscontrol syndrome (200,201). Thus, incarcerated inmates with impulsive-aggressive behavior showed significant reductions in the frequency and intensity of aggressive acts, normalization of event-related potentials (ERPs) (i.e., increased P300 amplitude), and improved mood state measures during a six-week, double-blind, placebo-controlled trial of phenytoin (300 mg/day) (202,203). Further, inmates whose aggressive behavior was considered premeditated did not show improvement (203). Stanford et al. (199) corroborated and extended these findings in a double-blind, placebo-controlled, crossover study of a noninmate population. Individuals meeting previously established criteria for impulsive aggression were given phenytoin and placebo during separate six-week conditions. Compared with baseline and placebo, the frequency of impulsive-aggressive outbursts significantly decreased during phenytoin treatment. Phenytoin also affected sensory/attentional processing (measured by ERPs) as indicated by increased P1 amplitude, longer-evoked potential latencies, and the suggestion of reduced N1 amplitude. In a double-blind, placebo-controlled, parallel group design, impulsive-aggressive men were randomly assigned to one of four six-week treatments: phenytoin ($N = 7$), carbamazepine ($N = 7$), valproate ($N = 7$), or placebo ($N = 8$) (199). A significant reduction in impulsive aggression (as measured by the OAS global severity index) was found during all three AED conditions compared with placebo. Compared with phenytoin and valproate, there was a slightly delayed effect during carbamazepine treatment.

In sum, these findings suggest that phenytoin could have a significant impact in the control of impulsive aggression in mental health and criminal populations. Further, because the antiaggressive properties of phenytoin appear selective for impulsive aggression, it suggests that biological mechanisms may distinguish impulsive from premeditated aggression (204).

DISCUSSION

Effective treatment of impulsivity and aggression depends on determining the cause(s) of these behaviors and selecting treatments accordingly. Pharmacological treatments may reduce impulsivity or aggression and normalize arousal by reducing dopaminergic activity, enhancing serotonergic activity, shifting the balance of amino acid neurotransmitter from excitatory (glutamatergic) toward inhibitory (GABAergic) transmission, and/or reducing or stabilizing nonadrenergic effects. Pharmacological and nonpharmacological treatment, like behavioral strategies aimed at reducing aggressive or impulsive behavior, may be most effective for the long-term treatment of the underlying chronic or recurrent illness (114). In general, there is no treatment of choice for impulse control and cluster B personality disorders. Many drugs from different classes seem to offer some benefit to selected individuals depending on their symptom presentations. For example, BPD patients with prominent cognitive and/or perceptual distortion may respond to antipsychotics, while those with depressed mood may respond best to antidepressants. Biological and behavioral dimensions may underlie treatment response in personality disorder patients (4,21). There may be several developmental trajectories to impulsivity and aggression (e.g., ADHD, bipolar spectrum, and trait impulsivity) and various routes to altering motivational circuitry, like modulating of corticostriatal-limbic circuits. We suggest that core symptoms within disorders should be treated and appropriate outcome measures should be used to determine targeted treatment response.

On the basis of the evidence presented here, AEDs appear to be effective for treating the symptom domains of impulsivity and aggression across a wide range of psychiatric disorders and for impulse control and cluster B personality disorders in particular. It is suggested that interventions should be directed at the brain circuitry, which modulates core symptoms that may be shared across disorders rather than DSM diagnoses. In addition to core symptom domains like impulsivity, affective instability, and aggression, clinicians should identify comorbid conditions and associated symptoms related to brain systems as they can also influence overall treatment response. AEDs may be effective for the treatment of the brain circuitry related to impulsivity, aggression, comorbid affective instability, and traumatic arousal, by modulating GABA, glutamate, serotonin, and norepinephrine.

Since ICDs and cluster B personality disorders have been found to be highly comorbid with other psychiatric disorders, the most effective and best-tolerated medication may vary depending on the comorbidity (101). Thus, AEDs, traditionally used to treat bipolar disorder, can also be effective for ICDs and cluster B personality disorders when there are associated bipolar symptoms. When treating the core symptoms of impulsivity and aggression, the associated bipolar and mood lability symptoms may improve as well. Clinicians should treat target symptoms like impulsivity and aggression regardless of their overall diagnosis, while taking into account comorbid disorders (e.g., bipolar disorder, ADHD), associated symptoms, developmental trajectory, and family history. For example, while SSRIs may be effective in treating pathological gambling with a comorbid obsessive-compulsive spectrum disorder or obsessive-compulsive features, they may not be the optimal treatment of pathological gambling with comorbid ADHD or a bipolar spectrum disorder (205,206). Clinicians must be careful when treating patients at risk for bipolar disorder, as SSRI-induced manic behaviors could emerge in those with a history of, or at risk for, mania or hypomania (44). Thus, a mood-stabilizing

AED like valproate may be a better treatment option for ICD patients with a comorbid bipolar disorder.

Accordingly, BPD patients with comorbid bipolar II disorder or subclinical bipolar symptomology may benefit from mood-stabilizing AEDs, like carbamazepine, if irritability is pronounced (63). Preliminary data indicate personality disorders with aggressive behavior, and emotionally unstable character disorder with mood swings, respond to AEDs. A variety of personality factors and comorbid conditions overrepresented in BPD patients, like premenstrual syndrome, bulimia, agoraphobia, major affective disorder (e.g., bipolar II), and hypersomnia, often complicate the clinical picture. Depending on the mix of these factors, certain drugs may need to be avoided, nonstandard drug combinations may need to be used, and safer drugs may need to be used in place of more effective drugs (102).

The growing experience of psychiatrists in treating ICDs, cluster B personality disorders, and impulsivity and aggression across disorders should compliment the knowledge obtained from research. This will lead to a better understanding of the brain mechanisms underlying impulsive and aggressive symptom domains within DSM disorders and to more targeted treatments with improved outcomes.

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The following queries have arisen during the typesetting of your manuscript. Please answer these queries.

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Q2	Page: 4 AU: Edits OK *in* "Healthy . . . region" for clarity?
Q3	Page: 5 AU: OK to remove "BN" for "bulimia nervosa" and replace it with "bulimia" to avoid two-letter abbreviation?
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Q5	Page: 7 AU: OK to change "aggression" to "aggressive" in sentence "Kaufman et al. (60) described two patients . . . aggressive behaviors."
Q6	Page: 8 AU: In sentence "There are several psychotherapies . . . resistant to treatment" should the "and" be "as," with a preceding comma?
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Q15	Page: 7 ED: Should it be Personality Disorders?

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