Antiepileptic Drugs for the Treatment of Impulsivity

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Abstract: Evidence is reviewed here which suggests that antiepileptic drugs (AEDs) may be effective for the treatment of impulsivity across a range of psychiatric disorders and for impulse control and cluster B personality disorders in particular. AEDs may be effective for the treatment of the brain circuitry related to impulsivity, by modulating GABA, glutamate, serotonin, and norepinephrine. It is suggested that interventions should be directed at the brain circuitry which modulates core symptoms like impulsivity that may be shared across disorders, rather than the disorder itself. In addition to these core symptom domains, clinicians should identify comorbid conditions and associated symptoms related to brain systems as they can also influence overall treatment response. The increasing experience of psychiatrists in treating impulse control disorders, cluster B personality disorders, and impulsivity across disorders should complement the knowledge obtained from research. This will lead to a better understanding of the brain mechanisms underlying impulsive symptom domains within disorders and to more targeted treatments with improved outcomes.

Keywords: Antiepileptic drugs, anticonvulsant, impulsivity, borderline personality disorder, impulse control disorders, pathological gambling.

I) INTRODUCTION

Impulsivity

Impulsivity is a natural behavior 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[1]. Moeller et al. [2] 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” (p. 1784). The symptom of impulsivity is a significant public health problem as it can be manifested by self-injurious behavior, suicide, suicide attempts, substance abuse, accidents (e.g., motor vehicle), domestic violence, assault, and destruction of property [3-8]. Intervention can occur at the symptom, syndrome, or behavioral level.

Impulsive 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 (see Fig. 1). This is based on similarities in associated clinical features (e.g., age of onset, clinical course, comorbidity) and response to selective pharmacological treatment (e.g. selective serotonin reuptake inhibitors (SSRIs)), suggesting a high degree of overlap among disorders [9]. Further, impulsivity can be thought of as part of a compulsive-impulsive (see Fig. 2) dimensional model where impulsivity and compulsivity represent polar opposite complexes that can be viewed along a continuum of compulsive and impulsive disorders. One endpoint marks compulsive or risk-aversive behaviors characterized by overestimation of the probability of future harm, exemplified by obsessive compulsive disorder. The other endpoint designates impulsive action characterized by the lack of complete consideration of the negative results of such behavior, exemplified by borderline and antisocial personality disorders.

It is suggested that interventions be directed at the brain circuitry which modulates core symptoms like impulsivity that may be shared across disorders, rather than the DSM diagnosis. The evidence presented here suggests that antiepileptic drugs (AEDs) are effective for treating the symptom domain of impulsivity across a wide range of psychiatric disorders and for impulse control and cluster B personality disorders in particular. However, clinicians must still remain cautious as impulsivity is not necessarily a unitary construct. For example, impulsivity observed in bipolar disorder may not be the same phenomenon as impulsivity observed in the context of antisocial personality disorder.

Evidence from studies of human personality suggests that impulsivity may be made up of several independent factors [1]. There seems to be not just one unitary “impulsivity” or only one type of impulsive behavior, instead there appears to be several related phenomena that are usually classified together as impulsivity and that lead to different forms of impulsive behavior which may be influenced by different biological mechanisms. Thus, different facets of impulsivity may relate to different areas of the brain, specifically within the prefrontal cortex (PFC). Until we know more about the
specific facets of impulsivity and how they relate to underlying neurobiology, clinicians should remain cautious when treating impulsivity across disorders and not simply apply the same treatment uniformly. In addition to core symptom domains like impulsivity, affective instability, and aggression, clinicians should identify comorbid conditions and associated symptoms related to brain systems, and the developmental trajectory and family history as they can also influence overall treatment response.

**Neural Substrates**

There are many contributing factors to impulsivity such as genes, gender, environment, psychiatric disorders, and substance abuse. The neurobiology of impulsivity and compulsivity may involve inhibitory neurotransmitters like serotonin and gamma-aminobutyric acid (GABA), excitatory neurotransmitters like glutamate, norepinephrine, and dopamine, and PFC and/or limbic dysfunction.

Convergent evidence suggests that a failure in top-down cortical control mechanisms, leading to striatal overdrive, may constitute a unifying pathophysiological model underpinning an ‘impulsive-compulsive spectrum’ of mental disorders [10]. The orbitofrontal cortex (OFC), with its extensive reciprocal connections with the amygdala (implicated in emotional behavior [11,12]), may play a role in correcting/regulating emotional and behavioral responses [13-17]. Limbic-orbitofrontal circuit dysfunction may be involved in impulsivity, at least in a subgroup of patients [18]. Impulsivity may involve increased limbic discharge, decreased OFC function, and/or hypoactive frontolimbic circuitry [19]. 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 based on stimulus-reinforcement associations [11,20-23]. 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 behaviors.

**Antiepileptic Drugs**

The AEDs valproate, carbamazepine, and lamotrigine have US Food and Drug Administration (FDA) indications for the treatment of bipolar disorder/mania. Other AEDs like oxcarbazepine, gabapentin, topiramate, levetiracetam, phenytoin, and tiagabine, often act as mood stabilizers but do not have FDA indication for bipolar disorder/mania. Use of AEDs off-label 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 [24]. Side effects from AEDs are typically mild to moderate. Common side effects include drowsiness, nausea/upset stomach, rash, and weight gain or loss (depending on the specific AED). Although data in regard to longer term safety in the newer AEDs are limited, they may have more desirable side-effect profiles.

Currently, anti-impulsive medication classes include SSRIs, serotonin (5-HT)1A agonists, 5-HT2 antagonists (see Table 1), lithium, anticonvulsants, atypical and typical neuroleptics, β-blockers, α2-agonists (e.g., clonidine, guanfacine), opiate antagonists (e.g., naltrexone), and dopamine agonists (e.g., stimulants, bupropion). Evidence is reviewed here which suggests that antiepileptic drugs (AEDs) may also be effective for the treatment of impulsivity across a range of psychiatric disorders. AEDs are increasingly used as primary or adjunctive treatments for impulse control disor-
Antiepileptic Drugs for the Treatment of Impulsivity  

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II). AEDS AND IMPULSIVITY ACROSS DIAGNOSES

AEDs have received preliminary exploration in the treatment of impulse control in a number of psychiatric disorders (see Table 2). The efficacy of AEDs for the treatment of impulsivity in patients without a seizure disorder remains to be established, with the possible exceptions of carbamazepine and valproate, which have been studied for this purpose in double-blind, placebo-controlled trials [25-27].

Divalproex Sodium

Divalproex sodium (DVP; a.k.a. valproic acid, valproate (VPA)), a GABA enhancer first introduced as an AED in 1967, is approved for use as an anticonvulsant and mood stabilizer. The literature, as far back as 1988, including several double-blind, placebo-controlled studies [7,25,28-30], supports the use of DVP in the treatment of impulsivity, hostility/aggression, impulsive aggression and affective instability in impulsive patients in a variety of psychiatric disorders. VPA has been reported to be effective against impulsive aggression and/or hostility in BPD subjects [7,25,28,29,31-35], and adolescents with aggression and labile mood in one open [36] and one controlled [37] study. Improved behavioral dyscontrol and aggression with DVP has also been noted in patients with post-traumatic stress disorder [38-40], temper outbursts [36,37,41], traumatic brain injury [42-43], dementia [31,44-46], and autism [47].

In a retrospective study [47], 14 patients with DSM-IV diagnosed autism, Asperger’s disorder, or pervasive developmental disorder not otherwise specified, with or without a history of seizure disorders or EEG abnormalities, were openly treated with VPA. Ten (71%) of the 14 patients had a sustained response to VPA, assessed by the CGI-I scale, which was generally well tolerated. Improvement was observed in core symptoms of autism (social interaction, speech/communication skills, repetitive behaviors) and associated features of affective instability, impulsivity, and aggression. However, given that this was an open retrospective study, these findings must be cautiously interpreted.

A subsequent controlled trial was conducted which found no treatment difference between groups in a prospective, 8...
Table 2. Trials of AEDs in Impulsivity Across Diagnoses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Sample</th>
<th>Method</th>
<th>Results</th>
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<tbody>
<tr>
<td>divalproex</td>
<td>Wilcox 1995 [34]</td>
<td>BPD inpatients (n=30)</td>
<td>6-week, naturalistic, OL</td>
<td>BPRS scores (particularly the anxiety sub-components), aggressive outbursts, and time in seclusion decreased</td>
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<td>sodium</td>
<td>Hollander et al 2001 [28]</td>
<td>BPD (n=16)</td>
<td>10-week, parallel, DB, PC</td>
<td>significant improvement from baseline in global measures (CGI-Improvement and GAS) and core symptoms</td>
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<td>Hollander et al 2001 [47]</td>
<td>Autism, Asperger’s, PDD-NOS (n=14)</td>
<td>Retrospective, OL</td>
<td>10/14 (71%) with sustained response (CGI-Improvement)</td>
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<td>Hollander et al 2003 [7]</td>
<td>Cluster B PD (n=96), IED (n=116), PTSD (n=34)</td>
<td>12-week, randomized, DB, PC</td>
<td>no treatment effect in last 4 weeks of OAS-M Aggression scores in intent-to-treat data set combined across disorders</td>
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<td>treatment effect observed in intent-to-treat and evaluable data sets for Cluster B PD patients</td>
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<td>in large subgroup of Cluster B PD patients, divalproex superior to placebo in impulsive aggression, irritability, and global severity</td>
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<td>Hollander et al 2005 [29]</td>
<td>BPD (n=52)</td>
<td>12-week, randomized, DB, PC</td>
<td>divalproex superior to placebo in reducing impulsive aggression</td>
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<td>divalproex patients responded better among those with higher baseline trait impulsivity and state aggression symptoms</td>
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<td>Simeon et al 2007 [32]</td>
<td>BPD (n=20)</td>
<td>12-week, OL</td>
<td>7/10 (70%) were treatment responders (CGI-Improvement endpoint of 2 (much improved) or 1 (very much improved))</td>
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<td>treatment associated with significant improvement in the CGI-I, GAS, OAS-M Irritability, Aggression Questionnaire</td>
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<td>Porsteinsson et al 2001 [44]</td>
<td>nursing home patients with agitation and dementia (n=56)</td>
<td>6-week, PC</td>
<td>68% on divalproex vs. 52% on placebo rated as showing reduced agitation on CGI</td>
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<td>significant difference in BPRS agitation scores for 2 treatment groups</td>
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<td>side effects in 68% of treatment group and 33% of placebo group, generally rated as mild</td>
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<td></td>
<td>Porsteinsson et al 2003 [46]</td>
<td>nursing home patients with agitation and dementia (n=56)</td>
<td>6-week, OL extension of [44]</td>
<td>mean BPRS agitation decreased by 3.1 points from baseline</td>
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<td>86% of completers rated as improved on CGI</td>
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<td>60% had no side effects, 33% had mild side effects</td>
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<td>Hellings et al 2005 [48]</td>
<td>PDD children aged 6-20 (n=30)</td>
<td>8-week, DB, PC</td>
<td>no treatment difference observed between groups</td>
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<td>Stanford et al 2005 [103]</td>
<td>impulsive aggressive men (n=29)</td>
<td>6-week, DB, PC, parallel; randomized to phenytoin (n=7), carbamazepine (n=7), valproate (n=7), or placebo (n=8)</td>
<td>significant reduction in impulsive aggression in all 3 treatment groups versus placebo</td>
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<td>treatment effect during carbamazepine administration slightly delayed compared with phenytoin and valproate</td>
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<td>Barzman et al 2006 [49]</td>
<td>adolescents with comorbid bipolar disorder and disruptive behavior disorders (n=33)</td>
<td>28-day, randomized, DB trial of divalproex vs. quetiapine</td>
<td>quetiapine and divalproex showed similar efficacy for impulsivity and reactive aggression</td>
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<td>Drug</td>
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<td>Saxena et al 2006 [51]</td>
<td>- 24 bipolar offspring (ages 6-18) with mixed diagnoses of MDD, cyclothymia, ADHD, and ODD (high risk for bipolar disorder)</td>
<td>- 12-week, OL</td>
<td>- 71% considered responders by the OAS</td>
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<td>Steiner et al 2007 [53]</td>
<td>- PTSD in CD youth (n=12)</td>
<td>- randomized (high and low dose divalproex), controlled</td>
<td>- significant positive associations between receiving high dose of divalproex and CGI ratings</td>
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<td>- those receiving high dose showed reduced severity of illness and greater improvement than low dose subjects</td>
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<td>carbamazepine</td>
<td>Mattes 1990 [62]</td>
<td>- temper outbursts in diverse diagnoses (n=80)</td>
<td>- randomized (carbamazepine vs. propranolol)</td>
<td>- diagnosis of IED predicted preferential response to carbamazepine</td>
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<td>Kafantaris et al 1992 [58]</td>
<td>- aggressive and explosive CD children, aged 5-10 (n=10)</td>
<td>- OL</td>
<td>- treatment associated with significant declines in target symptoms of aggressiveness and explosiveness</td>
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<td>Chatham-Showalter 1996 [57]</td>
<td>- combative patients with multiple trauma including traumatic brain injury (n=7)</td>
<td>- OL</td>
<td>- clinical decrease in combativeness within 4 days after treatment</td>
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<td>Cueva et al 1996 [59]</td>
<td>- aggressive and explosive conduct disordered children, aged 5-12 (n=22)</td>
<td>- 6-week, parallel, DB, PC</td>
<td>- carbamazepine was not superior to placebo ; untoward effects associated with carbamazepine were common</td>
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<td>Azouvi et al 1999 [56]</td>
<td>- patients presenting agitation and anger outbursts following severe closed head injury (n=10)</td>
<td>- 8-week, OL</td>
<td>- significant improvement in group score from six target items on neurobehavioral rating scale in areas of irritability and disinhibition</td>
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<td>Stanford et al 2005 [103]</td>
<td>- impulsive aggressive men (n=29)</td>
<td>- 6-week, DB, PC, parallel; randomized to phenytoin (n=7), carbamazepine (n=7), valproate (n=7), or placebo (n=8)</td>
<td>- significant reduction in impulsive aggression in all 3 treatment groups versus placebo</td>
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<td>oxcarbazepine</td>
<td>Mattes 2005 [68]</td>
<td>- impulsive aggression patients without other psychiatric symptoms (n=48)</td>
<td>- 4-weeks, DB, PC</td>
<td>- oxcarbazepine effective as shown on Global Overt Aggression rating derived from OAS-M and patient rated global improvement</td>
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<td>topiramate</td>
<td>Appolinario et al 2002 [78]</td>
<td>- BED patients with obesity (n=8)</td>
<td>- 16-week, OL</td>
<td>- of 6 completers, 4 patients presented total remission, and 2 had marked reduction in binge eating frequency</td>
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<td>- days with binge episodes per week and scores on the binge eating scale decreased significantly</td>
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<td>- significant weight los</td>
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<td>Janowsky et al 2003 [72]</td>
<td>- Institutionalized intellectually disabled adults (n=22)</td>
<td>- Retrospective, OL</td>
<td>- decreases in global severity scores and in the cumulative aggression and worst behavior rates</td>
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<td>Smathers et al 2003 [71]</td>
<td>- PWS (n=8)</td>
<td>- OL</td>
<td>- positive treatment effect on self-abusive behavior, weight, and mood</td>
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<td>Drug</td>
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<td>Method</td>
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<td>phenytoin</td>
<td>McElroy et al 2003 [74]</td>
<td>BED patients with obesity (n=61)</td>
<td>14-week, randomized, DB, PC</td>
<td>43 patients receiving at least one dose of topiramate provided outcome measures; mean weekly binge frequency declined significantly from baseline to final visit in all 43 patients; all exhibited significant reduction in body weight</td>
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<td>McElroy et al 2004 [79]</td>
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<td>levetiracetam</td>
<td>Zilberstein et al 2004</td>
<td>BED patients with inadequate weight loss after adjustable gastric banding (n=16)</td>
<td>12-week, OL.</td>
<td>mean increase in excess weight loss without the need for band readjustment; 2 patients exhibited topiramate intolerance</td>
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<td>levetiracetam</td>
<td>Nickel et al 2005 [84]</td>
<td>Bulimia nervosa (n=30)</td>
<td>10-week, randomized, DB, PC</td>
<td>topiramate treatment effective in reducing binge/purge frequency and body weight</td>
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<td>gabapentin</td>
<td>Dolengevich et al 2006 [87]</td>
<td>child and adolescent outpatients with impulsive behavioral disorders (n=11)</td>
<td>OL</td>
<td>significant differences in cognitive impulsivity subscale and total score of BIS after one month and the motor impulsivity subscale after 3 months</td>
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<td>Ruggino et al 2002 [88]</td>
<td>autistic male children aged 4 to 10 (n=10)</td>
<td>OL</td>
<td>treatment significantly reduced hyperactivity, impulsivity, mood instability, and disruptive outbursts</td>
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<td>Grunze et al 2003 [89]</td>
<td>bipolar I, acutely manic (n=10)</td>
<td>on-off-on design, OL add-on to haloperidol</td>
<td>mean decrease in YMRS ratings during first “on” phase, increase in symptoms during “off” phase, decrease during second “on” phase</td>
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<td>Simon et al 2004 [91]</td>
<td>social anxiety disorder, generalized type (n=20)</td>
<td>8-week, OL, flexible dose</td>
<td>significant decrease in LSAS scores in intent-to-treat, last-observation-carried-forward analysis; significant reductions in CGI-Severity and HRSA scores</td>
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<td>Wasserman et al 2006 [92]</td>
<td>autistic children, ages 5 to 17 (n=10)</td>
<td>10-week, DB, PC</td>
<td>no significant difference between treatment and placebo groups in terms of change in CGI-Improvement, Aberrant Behavior Checklist, Children’s Y-BOCS, or Conners’ scales</td>
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<td>phenytoin</td>
<td>Cherek et al 2004 [97]</td>
<td>adult parolees with antisocial behavior (n=20); 10 with history of CD</td>
<td>experimental sessions using the Point Subtraction Aggression Paradigm</td>
<td>gabapentin treatment produced similar bi- tonic effects on aggressive and escape responses for subjects with and without a history of CD</td>
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<td>phenytoin</td>
<td>Barratt et al 1997 [108]</td>
<td>incarcerated inmates with impulsive-aggressive behavior (n=60)</td>
<td>6-week, DB, PC, CO</td>
<td>phenytoin reduced impulsive-aggressive acts but not premeditated aggressive acts</td>
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<td>phenytoin</td>
<td>Stanford et al 2001 [104]</td>
<td>impulsive-aggression patients (n=23)</td>
<td>DB, PC, CO (6-week conditions)</td>
<td>significant decrease in frequency of impulsive-aggressive outbursts during phenytoin administration compared to baseline and placebo</td>
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Notes: BPD=borderline personality disorder; OL=open-label; BPRS=Brief Psychiatric Rating Scale; DB=double-blind; PC=placebo-controlled; CGI=Clinical Global Impressions-Improvement Scale; GAS=Global Assessment Scale; PDD-NOS=pervasive developmental disorder—not otherwise specified; PD=personality disorder; IED=Intermittent Explosive Disorder; PTSD=posttraumatic stress disorder; OAS-M=Overt Aggression Scale-Modified; MDD=major depressive disorder; Notes: BPD=borderline personality disorder; OL=open-label; BPRS=Brief Psychiatric Rating Scale; DB=double-blind; PC=placebo-controlled; CGI=Clinical Global Impressions-Improvement Scale; GAS=Global Assessment Scale; PDD-NOS=pervasive developmental disorder—not otherwise specified; PD=personality disorder; IED=Intermittent Explosive Disorder; PTSD=posttraumatic stress disorder; OAS-M=Overt Aggression Scale-Modified; MDD=major depressive disorder; ADH=attention deficit hyperactivity disorder; ODD=oppositional defiant disorder; OAS=Overt Aggression Scale; CD=conduit disorder; KAS=Katz Adjustment Scale; BED=Binge Eating Disorder; PWS=Prader-Willi Syndrome; BIS=Barratt Impulsivity Scale; YMRS=Young Mania Rating Scale; LSAS=Liebowitz Social Anxiety Scale; HRSA=Hamilton Rating Scale for Anxiety; Y-BOCS=Yale-Brown Obsessive Compulsive Scale
week, randomized, double-blind, placebo-controlled study of 30 (20 boys) pervasive developmental disorders outpatients (aged 6-20) with significant aggression [48]. The side effects observed were mild. However, these negative findings should also be considered cautiously given the subject heterogeneity, large placebo response, and small sample size. The authors suggest that a more homogeneous subgroup of subjects with aggression accompanied by bipolar symptoms or mood lability may be more likely to respond to VPA.

In a randomized, double-blinded, 28 day study, quetiapine and DVP showed similar efficacy for the treatment of impulsivity and reactive aggression related to co-occurring bipolar and disruptive behavior disorders in adolescents (N=33) [49] and both were well tolerated. This trial was not placebo controlled, it was a relatively small sample size (16/17 patients per group at end point) and the patients were hospitalized with acute episodes of mania and mixed mania so the findings may not be generalizable to patients with less severe baseline agitation.

Barzman et al (2005) [50] 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. Significant improvements were obtained in response to DVP 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. Still, this was a retrospective study without a control group or randomization and the non-blinded design is subject to rater bias.

In a 12-week, DVP open-label trial in 24 bipolar offspring ages 6-18 (17 boys) with mixed diagnoses of major depression, cyclothymia, attention deficit-hyperactivity disorder (ADHD), and oppositional defiant disorder, 71% of subjects were considered DVP responders by the OAS [51]. Thus, youths who were at high risk for bipolar disorder experienced an overall decrease in aggressive behavior in response to DVP. The limitations of this study include its lack of a control group, relatively small sample size, diagnostically heterogeneous sample and open design which may have biased the raters. In another study, 3 boys with ADHD associated with giant somatosensory evoked potentials all responded well to VPA extended-release [52], with particular improvement in hyperactivity and impulsivity. Conversely, symptoms worsened when methylphenidate was previously administered to 2 of the patients.

In a recent randomized controlled trial, subjects were randomized into high and low dose DVP conditions for the treatment of PTSD in youth, in the context of conduct disorder (N=12) [53]. Intent-to-treat analyses showed significant positive associations between receiving high dose of DVP and CGI ratings. Subjects on a high dose of DVP achieving therapeutic blood levels showed reduced severity of illness and greater improvement than subjects who received minimal doses and showed a significantly greater increase in Restraint and decrease in Impulsivity as measured by the Weinberger Adjustment Inventory [54]. This was the first randomized psychopharmacological study of PTSD in youth, and raters were blinded to diagnoses and dose-condition, so assessment was not biased. But, outcome measures were not PTSD specific, all disorders were not assessed via structured interview, the sample size was small, and there was significant comorbidity of conduct and other disorders, so improved PTSD symptoms may have been due to improved symptoms in comorbid disorders. Finally, this was an all-male sample of incarcerated youth making generalized to non-incarcerated females adolescents difficult.

Prospective, randomized, double-blind, placebo-controlled trials of VPA are needed to further assess its optimal usage for the treatment of 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 epileptic patients with aggressive outbursts and irritability and temporal lobe epilepsy [55]. Carbamazepine has also been effective in decreasing combative, agitated behavior, irritability and disinhibition in subjects with head injuries [56,57]. However, although one open-label study of inpatient children with conduct disorder found statistically and clinically significant declines of explosiveness and aggression [58], a double-blind, placebo-controlled trial found no difference between carbamazepine and placebo, and side effects were common [59]. The few placebo-controlled trials with carbamazepine have been small and in diverse patient populations [60,61].

Matus [62] 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. Freymann et al (2005) [63] describe the successful use of carbamazepine in a 78-year old Alzheimer’s Disease patient with hypersexual behavior. The efficacy of carbamazepine in this case supports the important role of AEDs in the management of behavioral disturbances in demented patients.

Munoz and Gonzalez Torres [64] describe a 28-year-old male who had an intensification of previous personality traits, sexual exhibitionism, promiscuity, aggressive episodes, suspiciousness, and low impulse control after a severe brain injury in a car accident. Neuroleptics, benzodiazepines, and antidepressants had no effect. After two months of carbamazepine treatment, the patient had marked improvement with the absence of exhibitionistic behavior and aggressive episodes, a tendency towards normalization of mood and anxiety, stabilization of his social and family relationships, and employment. Morikawa et al. [65] report a 19-year-old male who had a personality change, marked by irritability, aggression, labile moods, childishness, irresponsibility, and lack of motivation, 6 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 pre-injury personality. After clonazepam was discontinued he maintained his good...
mental status and at 2 year follow he had no relapses. Lewin and Sumners [66] describe an 18-year-old man who, follow-
ing a traffic accident, developed episodic dyscontrol. Two
years post-injury, carbamazepine treatment was started and
his impulsive aggressive outbursts subsided.

Oxcarbazepine, a more recent AED structurally similar to
carbamazepine, appears, like carbamazepine, to be helpful for
temporal lobe (or complex partial) seizures, and may also
have mood-stabilizing effects [67]. In a double-blind, pla-
cebo-controlled, 10 week study, adult outpatients with clini-
cally significant impulsive aggression were randomized to
placebo (N=24) or oxcarbazepine (N= 24) [68]. Nine patients
dropped out due to adverse events, but 45 completed at least
4 weeks. Results showed a benefit from oxcarbazepine com-
pared with placebo on OAS-M scores and patient-rated global
improvement. Cordas et al (2006) [69] describe 2 cases of
severe bulimia nervosa and BPD, in which self-mutilating
behavior was successfully controlled after oxcarbazepine
treatment.

**Topiramate**

Topiramate, a newer AED which acts on voltage-activated
sodium channels and glutamate and GABA receptors, has
been reported to be effective in aggressive patients [70] [71].
In an open-label retrospective (chart review) study, Janowsky
et al. [72] examined topiramate treatment in 22 severely or
profoundly intellectually disabled, institutionalized adults,
most with a concurrent mood disorder. Patients were treated
for aggression, self-injurious behaviors, destruc-
tive/disruptive behaviors or a combination of these, and/or
other challenging and maladaptive behaviors. Significant
decreases in global severity scores, cumulative aggression,
and worst behavior rates occurred, especially when comparing
the 3 months before and 3 to 6 months after starting topi-
ramate. Again, since this was an open-label retrospective
study, rater bias may have skewed the results.

Impulsivity plays a significant role in a wide range of
psychiatric disorders including eating disorders like binge
eating disorder (BED). Topiramate has also shown efficacy in the treatment of a number of disorders involving impulsivity includ-
ing BED [73,74]. BED is characterized by recurrent
episodes of binge eating that are not following with regular
use of inappropriate compensatory weight loss behaviors and
is usually associated with overweight or obesity and psycho-
pathology. Antidepressants (tricyclics, SSRIs, noradrenaline
re-uptake inhibitors) are the best studied medications in BED
and may reduce depressive symptoms and augment psycho-
therapy. The literature offers support, including double-blind,
placebo controlled trials, for the use of antidepressants, appet-
ite suppressants (e.g. sibutramine), and AEDs in the treat-
ment of BED [75-77]. Topiramate in particular appears to be
promising for the treatment of BED. This makes sense since
BED is associated with obesity, and topiramate is associated
with reduced appetite and weight loss in clinical trials for
other psychiatric disorders and epilepsy.

In a naturalistic, open-label study with topiramate, 9 of
13 BED outpatients showed a moderate or better response of
BED symptoms after beginning treatment that was main-
tained for 3 to 30 months [73]. Two other patients had mod-
erate or marked responses that subsequently diminished and
the remaining 2 patients had a mild or no response. In an-
other open label study, treatment with topiramate (150 mg
daily) was administered over 16-weeks to 8 obese patients
with BED and no medical or psychiatric comorbidity [78].
All 6 of the trial completers showed reduced binge eating.
Four patients had a total remission, and 2 had a marked re-
duction in binge eating frequency. Patients also had signifi-
cant weight loss.

In a 14-week, double-blind, flexible-dose topiramate trial,
BED outpatients were randomly assigned to receive topi-
ramate (N=30) or placebo (N=31) [74]. Compared with pla-
cebo, topiramate resulted in a significantly greater rate of
reduction in binge frequency, binge day frequency, body mass
index (BMI), weight, and scores on the CGI-S and the Yale-
Brown Obsessive Compulsive Scale (Y-BOCS) modified for
binge eating (Y-BOCS-BE). McElroy et al. [79] also found
that topiramate had positive effects for the long term treat-
ment of BED in a 42-week, open-label extension trial of
topiramate. For all patients (N=43) receiving topiramate dur-
ing either the double blind or open label extension study,
there was a significant decline from baseline to final visit in
weekly binge frequency, CGI-S, Y-BOCS-BE (total and
compulsion and obsession subscale scores), weight, and
BMI.

Zilberstein et al. [80] analyzed 16 patients with binge
eating and inadequate weight loss after adjustable gastric
banding while receiving topiramate for 3 months (12.5 to 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 could not tolerate topiramate. Dolberg et al.
[81] report the effects of topiramate, on top of ongoing
Treatment, on eating patterns and weight of 17 patients with
traumatic brain injury, post-traumatic epilepsy, and weight
gain of various etiologies. Six BED patients had the most
pronounced effects, with marked decreases in binges and a
normalization of BMI. In another study, 3 obese BED pa-
ients, who had recurrent binge eating and weight gain after
initially successful bariatric surgery, reported complete im-
provement of their binge eating and displayed weight loss
after receiving topiramate for 10 months on average [82]. De
Bernardi et al. [83] report a BED patient who was unrespon-
sive 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 [84].

Topiramate may also be effective in treating self-
mutilating behavior. Topiramate improved self-mutilation and
manic symptoms in 2 patients with bipolar disorder and
BPD [85]. Further, topiramate (200 mg/day; on-off-on de-
sign) administered to a 24-year-old woman with bipolar-II
major depression and BPD, led to long-term remission of
self-mutilation, despite the persistence of depression [86]. No
self-injurious acts occurred over 9 months, and mood was
sufficiently stabilized.

Dolengevich et al (2006) [87] evaluated 11 child and ado-
slescent outpatients with impulsive behavioral disorders
(DSM-IV criteria) at zero, one, and three months after start-
ing topiramate treatment. There were significant differences
in the cognitive impulsivity subscale and total score of the
Baratt Impulsivity Scale after one month, and the motor
impulsivity subscale after 3 months. Thus, topiramate may
be an effective treatment for impulsivity in adults with psy-
chiatric disorders, as well as in childhood and adolescents, but blinded controlled study is needed.

In sum, although the results appear promising, many of the studies conducted thus far with topiramate and disorders involving impulsivity were open label and uncontrolled. Thus, more blinded studies with larger samples and placebo controls are needed to confirm the efficacy of topiramate for the treatment of impulsivity.

Levetiracetam

There is preliminary evidence that levetiracetam (LEV), FDA-approved as an adjunctive treatment for partial-complex seizures, may have efficacy in a spectrum of psychiatric disorders characterized by affective lability, impulsivity and anxiety [88-91]. In an open-label prospective study of 10 autistic boys aged 4 to 10, LEV significantly reduce hyperactivity, impulsivity, mood instability, and disruptive outbursts [88]. However, in a 10-week, placebo-controlled, double-blind trial of LEV in 20 autistic children ages 5 to 17, no significant difference was found between LEV and placebo groups in terms of change in CGI-I, Aberrant Behavior Checklist, Children's Y-BOCS, or Conners's scales [92]. These findings suggest that LEV does not improve 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, LEV has actually increased aggression as a side effect [93-96]. In sum, the effect of LEV on impulsivity, mood instability, and aggression is unclear and further studies are warranted. However, behavioral tolerability of LEV should be monitored carefully, especially in patients with a history of aggression.

Gabapentin

Gabapentin is an anticonvulsant which is able to moderately increase GABA, a neurotransmitter important for the neurochemical control of aggressive behavior [97]. Alkhail et al. [98] describe 3 dementia nursing home residents whose sexual disinhibition was effectively treated with gabapentin. McManaman & Tan (1999) [99] describe a patient with Lesch-Nyhan syndrome (an X-linked disorder of purine metabolism) whose self-injurious behavior was effectively treated with gabapentin. Gupta et al (2000) [100] describe a patient with DSM-IV diagnosed conduct disorder resulting in aggression and violent behavior whose symptoms were controlled with gabapentin after he had failed a trial of DVP. In another case [101], 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 closed head injury, and simple partial seizure disorder. Cherek et al. [97] measured aggression in 20 adult parolees (2 females) with a pattern of antisocial behavior, using the Point Subtraction Aggression Paradigm, which provided aggressive, escape, and monetary reinforced response options. Ten subjects had a history of childhood conduct disorder (CD+) and ten had no history (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). 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, indicating an absence of CNS stimulation or sedation. Controlled blinded studies of gabapentin are needed before anything can be said of its possible effect on impulsivity.

Phenytoin

Phenytoin has been shown to reduce the frequency of impulsive-aggressive behavior [102,103], alter mid-latency evoked potentials [104], and significantly reduce violent outbursts in psychiatric patients with episodic dyscontrol syndrome [105,106]. Accordingly, incarcerated inmates with impulsive aggressive behavior showed significant reductions in the frequency and intensity of aggressive acts, normalization of event-related potentials (ERPs) (increased P300 amplitude), and improved mood state measures during a 6-week, double-blind, placebo-controlled trial of phenytoin (300 mg/day) [107,108]. Further, inmates whose aggressive behavior was considered premeditated did not show improvement [108]. Stanford et al. [104] corroborated and elaborated these findings in a double-blind, placebo-controlled, crossover study of a non-inmate population. Individuals meeting previously established criteria for impulsive aggression were given phenytoin and placebo during separate 6-week conditions. Compared to 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 1 of 4 six-week treatments: phenytoin (N=7), carbamazepine (N=7), VPA (N=7), or placebo (N=8) [103]. A significant reduction in impulsive aggression (OAS global severity index) was found during all 3 AED conditions compared with placebo. But, compared with phenytoin and VPA, there was a slightly delayed effect during carbamazepine treatment. Thus, carbamazepine and VPA may be as effective as phenytoin in reducing impulsive aggression.

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 [109].

III). AEDS AND CLUSTER B PERSONALITY DISORDERS

A). Borderline personality Disorder

The majority of AED treatment studies across cluster B personality disorders focus specifically on BPD. 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 [110] classifies BPD as an axis II cluster B Personality Disorder with criteria that includes affective instability, impulsive risk taking be-
behavior, inappropriate and intense anger, fear of abandonment, unstable relationships rapidly shifting between idealization and devaluation, unstable self image, feelings of emptiness, dissociative experiences, self-injurious behavior like superficial skin cutting or burning, and multiple suicide attempts. A typical symptom for BPD is the tendency to have outbursts of aggressive impulsivity [111]. The designation of BPD as an Axis II personality 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 and personality disorders have arisen, giving theoretical rationale for the investigation into the neurobiology of BPD.

BPD is generally characterized by affective instability (related to increased responsivity of the cholinergic system), impulsivity, and aggression (both related to reduced serotoninergic brain activity) and is associated with high levels of functional impairment, treatment utilization, and mortality by suicide [112,113]. Approximately 10% of patients with BPD commit suicide [114]. BPD has an estimated prevalence of 1-2% of the U.S. population [110,115-118], with men constituting only about 25% of patients [118], and it accounts for approximately 10% of all psychiatric outpatients and 20% of acute inpatient hospitalizations [110,119,120]. 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, pharmacotherapy may serve as a useful adjunct to psychotherapeutic interventions in BPD, and a combination of these approaches may be most effective [121,122].

In evaluating the use of medications for treating personality disorders, one can (1) treat the disorder itself; (2) treat associated axis I disorders; or (3) treat symptom clusters/psychobiologic dimensions within and across disorders [123]. 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 symptom clusters [123]. New and old antipsychotics (the most well documented), monoamine oxidase inhibitors (MAOIs), SSRI s, and AEDs are currently used for BPD [35]. 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 rapidly cycle, neuroleptics 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, Coryell (2005) [124] conclude that the combination of lithium and carbamazepine, valproate or lamotrigine for maintenance has some support from controlled studies, as does the adjunctive use of olanzapine. But placebo-controlled studies so far provide the most support for the use of lithium and lamotrigine as prophylactic agents. However, it appears that AEDs are used more widely than lithium in treating BPD.

Divalproex Sodium

Recently, AED trials have focused on DVP for efficacy in BPD. DVP has been shown to improve symptoms of irritability, agitation, aggression, and anxiety in patients with BPD [25,28,34,125-127]. In an open trial, 8 BPD patients completed an 8-week trial of VPA [127]. Half of the completers 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 SCL-90 scores. Wilcox [34] treated 30 BPD inpatients in a naturalistic open trial of VPA. Brief Psychiatric Rating Scale scores (particularly the anxiety subcomponents), aggressive outbursts, and time in seclusion significantly decreased during the 6-week trial. In addition to treating the aggressive and impulsive symptoms of BPD patients, DVP may also be helpful in treating BPD patients who report changeable mood (subsyndromal for major depression or hypomania) [33]. In a case series DVP treatment study, 6 of 9 BPD patients with mood instability (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 [33]. Responders showed a greater reduction in Hamilton Rating Scale for Depression scores than nonresponders. DVP extended-release was recently found to be efficacious and well-tolerated for BPD in a 12-week open-label trial of 20 adult DSM-IV diagnosed BPD outpatients [32]. Seven out of 10 completers (70%) were treatment responders, with an endpoint CGI-I of 2 (much improved) or 1 (very much improved) and there was a trend toward significant improvement on the Affective Intensity Measure. One patient discontinued due to adverse events. However, it must be kept in mind that all of these were open, uncontrolled trials which makes the findings far from conclusive.

In a preliminary, double blind trial, BPD outpatients were treated for 10 weeks with VPA (N=12) or placebo (N=4) [28]. There was significant improvement from baseline in measures of global symptom severity (CGI-I) and functioning (Global Assessment Scale) following treatment. A high dropout rate precluded finding significant differences between the treatment groups in the intent-to-treat analyses, although all results were in the predicted direction in that patients in the treatment group had a decrease in score on the Aggression Questionnaire and Beck Depression Inventory compared with placebo. Thus, DVP may be more effective than placebo for global symptomatology, level of functioning, aggression, and depression. These findings should be viewed with caution given the small sample size and high drop-out rate, but DVP was well tolerated in his sample and larger well-controlled trials are warranted.

In another controlled double-blind study of DVP, efficacy was examined in 30 women with comorbid BPD and bipolar II disorder over 6 months [25]. DVP, at an average dose of 850 mg/day (blood levels from 50 to 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. Limitations of this study include the small sample size, high drop-out rate, and all subjects were moderately ill outpatient men without concurrent major depression, substance abuse, or
medication, making it difficult to generalize to female BPD patients who are on concurrent medications and more severely ill. Finally, it is not known how much of the response was due to improvements in their BPD symptoms and how much was due to improvements in their bipolar symptoms.

Since DVP may improve impulsive aggression, irritability, and global severity in patients with cluster B personality disorders [7], Hollander et al. [29] examined clinical characteristics of BPD outpatients that might predict treatment response to DVP for impulsive aggression. In this randomized, double-blind, 12 week study, DVP (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 DVP relative to placebo. However, baseline affective instability did not affect differential treatment response. These data may be helpful in identifying patient subgroups (e.g., those with high levels of trait impulsivity or state aggression) or baseline characteristics of BPD 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 [72,128,129].

**Carbamazepine and Oxcarbazepine**

Carbamazepine, an anticonvulsant with primary effects on subcortical limbic structures, has been effective in the treatment of a wide range of psychiatric disorders, including classical affective disorders. Because patients with BPD show prominent affective symptomatology and symptoms suggestive of an epileptoid disorder, carbamazepine may 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 [130]. Limitations of this study include the small sample size, the highly selected patients group (outpatients with histories of behavioral dyscontrol), the relatively short observation period (6 weeks), and the fact that the degree of global improvement was often modest. In addition, 3 of these patients developed melancholia during carbamazepine treatment, which remitted on discontinuation of carbamazepins [131]. So, while carbamazepine may be an effective medication for some BPD patients, clinicians should be mindful of any changes in depressive symptoms.

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 16 female BPD outpatients with prominent behavioral dyscontrol and without current major depression [122]. But, given this cross-over design, a carryover effect between the different medications tested cannot be excluded. Subsequently, another carbamazepine study of 20 BPD inpatients without concurrent depression or comitant medications, yielded negative results [132]. After 4 weeks of treatment at standard doses, carbamazepine was no better than placebo in treating depression, behavioral dyscontrol or global symptomatology. However, the number of patients that reached endpoint in the carbamazepine group was small (only 8), and in the above mentioned Cowdry and Gardner study [122], carbamazepine was given for 42 days, while it was given for only for 32 days in this study. The positive trends observed in the carbamazepine group in this study may have reached significance with a longer administration period. In sum, the findings thus far for the treatment of BPD with carbamazepine are equivocal and more studies are needed. It should also be noted that carbamazepine requires close monitoring of drug levels and hematologic function to monitor for potentially hazardous side effects.

More recently, in an open-label study Bellino et al. (2005) [133] tested 17 DSM-IV-TR diagnosed BPD outpatients with oxcarbazepine, an AED structurally related to carbamazepine, typically used for treating patients with bipolar disorders, substance abuse, resistant psychosis, and schizoaffective disorder. Patients were administered 1200 to 1500 mg/day of oxcarbazepine, and tested at baseline, week 4, and week 12. Four patients discontinued treatment due to noncompliance. A significant response to oxcarbazepine was observed according to mean scores on the CGI-S, Brief Psychiatric Rating Scale, and Hamilton Rating Scales for Anxiety, and interpersonal relationships, impulsivity, affective instability, and outbursts of anger items and total score of the Borderline Personality Disorder Severity Index. Oxcarbazepine was well tolerated with no severe adverse effects. Thus, oxcarbazepine may be an effective and safe treatment for BPD patients. However, controlled studies are needed.

**Topiramate**

Treatment with topiramate for BPD has shown positive results in double blind placebo controlled trials. In an 8 week, double-blind placebo-controlled trial of topiramate to treat aggression in DSM-IV diagnosed BPD females, the topiramate group (N=19) showed significantly more efficacy than the placebo group (N=10) [134] as measured by 4 subscales of the State Trait Anger Expression Inventory (STAXI) scales (state-anger, trait-anger, anger-out, anger-control). Significant changes on the same four STAXI scales were also observed in DSM-IV diagnosed BPD males treated with topiramate (N=22) in an 8-week, double-blind, placebo (N=20) controlled study [135]. And the topiramate group experienced a significantly greater change than the placebo group on all STAXI scales in an 18 month open-label follow up to this study [136]. In both male and female BPD studies [134-136], topiramate was effective and well tolerated and significant weight loss was observed. This corresponds with other studies where topiramate therapy resulted in significantly decreased symptoms of aggression [70,72]. In terms of limitations of these studies, the sample sizes were small, all subjects were moderately ill outpatients without concurrent major depression, substance abuse, or medication, which may be an unrepresentative BPD sample, and the trials were relatively short (only 2) months which may have reduced the drop-out rate.

Loew et al. (2006) [137] explored whether topiramate could influence patients’ borderline psychopathology, health-related quality of life, and interpersonal problems. In this double-blind placebo controlled study, DSM-IV diagnosed BPD women were randomly assigned in a 1:1 ratio to topiramate titrated from 25 to 200 mg/d (n=28) or placebo (n=28) for 10 weeks. Patients on topiramate improved significantly on the broad spectrum of borderline symptoms and in their health-related quality of life and interpersonal problems. Significant weight loss was also observed. This double-blind, randomized controlled study supports topiramate’s efficacy.
for BPD, but the analysis was limited due to the relatively small sample size and the inclusion of only moderately ill BPD women without concurrent substance abuse or medication which make the findings hard to generalize [138]. Also, the length of this trial was only 10 weeks, which may have reduced the dropout rate. Further research with a more representative sample and relevant outcome measures are needed as well as studies to test how long-lasting the potential benefits of topiramate for BPD are. In terms of a proposed mechanisms, Do Prado-Lima et al (2006) [139] suggest that topiramate might facilitate memory extinction, thereby decreasing emotional and behavioral reactivity in BPD.

**Lamotrigine**

Several uncontrolled studies [140-142] and case studies [143,144] have suggested that lamotrigine may be effective for the treatment of BPD, but there has been only one double-blind placebo control study of lamotrigine for BPD to date. In this study Tritt et al (2005) [145] investigated the efficacy of lamotrigine in the treatment of aggression in BPD women. Subjects were randomly assigned in a 2: 1 ratio to lamotrigine (n = 18) or placebo (n = 9) for 8 weeks. In comparison with the placebo group, highly significant changes on four STAXI scales (state-anger, trait-anger, anger-out, anger-control) were observed in subjects treated with lamotrigine after 8 weeks. All the patients tolerated lamotrigine relatively well and it had no clinically significant effect on body weight. Limitations of this study include the relatively small sample size (despite valid power analysis), and the sample consisted only of moderately ill, female outpatients without substance abuse which limits the generalizability of these findings. In addition, this trial was only 2 months, which may have reduced the potential side-effects and dropout rate, especially in the placebo group.

In an 18-month follow-up observation study, these patients (lamotrigine group, n = 18; former placebo group, n = 9) (took neither lamotrigine nor placebo) were tested every six months [146]. The lamotrigine group experienced significantly greater changes on all STAXI scales compared to the ex-placebo group. All subjects tolerated lamotrigine relatively well. But, both the blind and placebo medication were discontinued and the relatively high dropout rate limits the generalizability of these findings. Further, these studies focused only on the aggressive impulsivity dimension of BPD. So the effects of lamotrigine on other dimensions of BPD, like affective dysregulation, disturbed relationships, and cognitive perceptual impairment remains to be investigated.

In sum, there is preliminary evidence that lamotrigine is relatively safe and may have efficacy in treating BPD, especially symptoms of anger and impulse control. Additional placebo-controlled trials of longer duration and of more representative samples are needed.

**B. Cluster B Personality Disorders**

Many researchers have suggested the use of AEDs for the treatment of the affective, impulsive, and aggression symptoms of cluster B personality disorders. The data thus far suggest that carbamazepine, VPA, and gabapentin are the most effective AEDs for the symptoms of cluster B personality disorders.

**Divalproex Sodium and Carbamazepine**

Stein [147] suggests 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 [114] suggests 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 [148] 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. According to Coccaro and Kavoussi [149], 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 a review, Pelissolo and Lepine [150] explain that for cluster B personality disorders, especially antisocial and BPD, positive results have been obtained using lithium, carbamazepine, and valproate, for dealing with aggressive and impulsive behaviors.

Hollander et al. [7] conducted a large, placebo-controlled, multi-center trial of DVP for the treatment of impulsive aggression in cluster B personality disorder, IED, or post-traumatic stress disorder. These different diagnoses were included as they have the common symptomatology of impulsivity and aggression, which could benefit from the 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 DVP; 48 placebo) of the 96 randomized cluster B personality disorder patients were included in the intent-to-treat data set (received at least one dose of the study drug and had at least one post-baseline OAS-M rating), and 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 placebo or DVP, 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 DVP was superior to placebo in the treatment of impulsive aggression, irritability, and global severity in a large subgroup of patients with cluster B personality disorders. A treatment effect was observed in both intent-to-treat and evaluable (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 4 weeks of treatment. In the cluster B evaluable data set, statistically significant treatment differences favoring DVP were also observed for component items of the OAS-M Aggression score (including verbal assault and assault against objects), OAS-M Irritability score, and CGI-S at multiple time points throughout the study. Across psychiatric diagnoses, 21 (17%) patients in the DVP group prematurely discontinued because of an adverse event, compared to 4 (3%) patients in the placebo group.

These results support findings from a previous double-blind placebo controlled trial [28] (described in detail above) which found decreased impulsive aggressive behavior and irritability in BPD patients treated with DVP. They also
support findings from an 8-week open trial of VPA, where 6 of 8 completers, with a diagnosis of at least one personality disorder who had failed a trial of a SSRI, showed significant decline in irritability and impulsive aggression on the OAS-M [126]. And, unlike another double-blind pilot study [25] (see above), where DVP was superior to placebo for the treatment of irritability and hostility in women with bipolar II and BPD, patients in Hollander et al. [7] were excluded if they had bipolar disorder I or II with recent hypomania (in the past year). Thus, the effect of DVP in impulsive aggression may be unrelated to its effect in mania. But, the possibility that the impulsive aggression of cluster B personality disorders has an affective component, or of a subclinical mood disorder in cluster B personality disorder patients, cannot be excluded.

The considerable placebo response and the low valproate serum levels and sample size may have contributed to the overall negative findings of this study. Further, the over-representation of males with outwardly directed aggression in the Cluster B population (63%) must be considered when making generalizations about these results to, for example, females and those with inwardly directed aggression (e.g., overdose, mutilation). Also, change from baseline impulsivity was not sufficiently measured by the OAS-M, and the OAS-M measures aggressive behaviors (verbal, and assault against others, objects, and self), but does not differentiate between qualitatively different subtypes of aggression (predatory, affective/impulsive). So, some of the patients in this trial may have had both predatory and affective aggression. Future trials should incorporate specific measurements of impulsivity, and try to discriminate between aggression subtypes, as they may have differential responses to treatment.

**Gabapentin**

Preliminary findings thus far suggest that gabapentin may be an effective mood stabilizer for the treatment of personality disorders but double-blind placebo controlled trials are needed. Gabapentin is an AED structurally similar to GABA, with unclear mechanisms of action and a good safety profile. Biancosino et al. [151] reported a case of successful gabapentin treatment of chronic impulsive aggressive behavior in a patient with severe BPD. In an observational study, Morana et al. [152] treated 29 cluster B personality disorder outpatients (8 antisocial; 13 impulsive type; 7 histrionic type; 1 narcissistic) with the maximal dose of gabapentin (1200 mg/day), alone or with other drugs (neuroleptics, mood stabilizers and benzodiazepines). After 6 weeks of treatment with gabapentin, 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 care givers. No other medication had such positive results on an equal number of patients. However, this study was not blinded or controlled and although diagnosis was established using international criteria (ICD10, DSM-IV), some of the patients were diagnosed using personality assessment instruments (Rorschach Proof and PCL-R) which may be less accurate.

Peris et al (2007) [153] investigated gabapentin in an open label multicenter 6-month follow-up trial in BPD patients not responsive to previous therapies. A global improvement, especially in anxious and depressive symptomatology, was observed and no adverse events were reported. In a review, Morana and Camara (2006) [154] found that after more than 4 years of studies 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 antisocial behaviors, as reported by the patient informers. The authors observed a decrease of aggressiveness, impulsiveness, offender behavior, and drug abuse, and a general improvement in tolerance, concentration, and prospective capacity, with larger interest for productive activities. Gabapentin may reduce excitability and turbulent behavior via its inhibitory effect in brain neurotransmission [155].

**Summary**

A symptom-specific method using current empirical evidence for drug efficacy in each symptom domain of BPD is proposed. Drugs in each medication class have some potential utility against specific symptoms of BPD [26]. 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, aggressive) rather than the disorder itself. Based on the above evidence (see Table 3 for a summary), it is suggested that selective AEDs may be effective in treating the affective, impulsive, and aggressive symptoms of BPD and the other cluster B personality disorders.

**IV. AEDS AND IMPULSE CONTROL DISORDERS**

IED, kleptomania, pyromania, pathological gambling (PG), trichotillomania, and ICDs not otherwise specified (NOS) are the classic disorders of impulse control grouped under “impulse-control disorders not elsewhere classified” in the Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision (DSM-IV-TR; [110]), 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 ICDs 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, bulimia), substance use disorders, schizophrenia, ADHD, paraphilias, conduct disorder, and neurological disorders with disinhibition.

There is gender predominance where certain ICDs, namely PG, IED, pyromania, and sexual compulsions, are more prevalent in males, and other ICDs, namely kleptomania, trichotillomania, self-injurious behavior, compulsive shopping, and binge eating disorder, are more prevalent in females. Both men and women express impulsivity but do so in different ways. It is unclear why, but it may be related to genetic factors, differences in serotonin turnover, hormonal differences, or social/environmental pressures. Treatment
Table 3. Trials of AEDs in Cluster B Personality Disorders

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Sample</th>
<th>Method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>divalproex sodium</td>
<td>Stein et al 1995 [127]</td>
<td>BPD (n=8)</td>
<td>8-week OL</td>
<td>50% rated as overall responders, with significant to modest decreases in depression, anxiety, anger, impulsivity, rejection sensitivity, and irritability (OAS-M and SCL-90)</td>
</tr>
<tr>
<td></td>
<td>Wilcox 1995 [34]</td>
<td>BPD inpatients (n=30)</td>
<td>6-week, naturalistic, OL</td>
<td>BPRS scores (particularly the anxiety subcomponents), aggressive outbursts, and time in seclusion decreased</td>
</tr>
<tr>
<td></td>
<td>Kavoussi &amp; Coccaro 1998 [126]</td>
<td>patients with at least one PD (n=10)</td>
<td>8-week, OL</td>
<td>6/8 completers reported decreases in irritability and impulsive aggressive behavior. For the entire sample, improvement on OAS-M irritability and overt aggression scores continued from the end of week four through week 8</td>
</tr>
<tr>
<td></td>
<td>Hollander et al 1998 [126]</td>
<td>BPD (n=10)</td>
<td>8-week, OL</td>
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</tr>
<tr>
<td></td>
<td>Hollander et al 2001 [28]</td>
<td>BPD (n=16)</td>
<td>10-week, parallel, DB, PC</td>
<td>Significant improvement from baseline in global measures (CGI-Improvement and GAS) and core symptoms</td>
</tr>
<tr>
<td></td>
<td>Frankenburg &amp; Zanarini 2002 [25]</td>
<td>comorbid BPD and bipolar II (n=30)</td>
<td>6-month, DB, PC</td>
<td>Divalproex well-tolerated and superior to placebo in diminishing interpersonal sensitivity and anger/hostility (SCL-90) and overall aggression (OAS-M)</td>
</tr>
<tr>
<td></td>
<td>Hollander et al. 2003 [7]</td>
<td>Cluster B PD (n=96), IED (n=116), PTSD (n=34)</td>
<td>12-week, randomized, DB, PC</td>
<td>No treatment effect in last 4 weeks of OAS-M Aggression scores in intent-to-treat data set combined across disorders. Treatment effect observed in intent-to-treat and evaluable data sets for Cluster B PD patients. In large subgroup of Cluster B PD patients, divalproex superior to placebo in impulsive aggression, irritability, and global severity</td>
</tr>
<tr>
<td></td>
<td>Hollander et al. 2005 [29]</td>
<td>BPD (n=52)</td>
<td>12-week, randomized, DB, PC</td>
<td>Divalproex superior to placebo in reducing impulsive aggression. Divalproex patients responded better among those with higher baseline trait impulsivity and state aggression symptoms</td>
</tr>
<tr>
<td></td>
<td>Simeon et al 2007 [32]</td>
<td>BPD (n=20)</td>
<td>12-week, OL</td>
<td>7/10 (70%) were treatment responders (CGI-improvement endpoint of 2 (much improved) or 1 (very much improved)). Treatment associated with significant improvement in the CGI-I, GAS, OAS-M Irritability, Aggression Questionnaire</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>Gardner &amp; Cowdry 1986 [131]</td>
<td>BPD (n=17)</td>
<td>DB, PC</td>
<td>3/17 patients developed melancholia, which remitted on discontinuation of carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Gardner &amp; Cowdry 1986 [130]</td>
<td>females with BPD (n=11)</td>
<td>DB, PC, CO</td>
<td>Decreased severity of behavioral dyscontrol in women receiving carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Cowdry &amp; Gardner 1988 [122]</td>
<td>female BPD patients with prominent behavioral dyscontrol (n=16)</td>
<td>6-week, DB, PC, CO</td>
<td>Treatment led to a dramatic, highly significant decrease in clinician rated behavioral dyscontrol, and had a modest effect on mood</td>
</tr>
<tr>
<td></td>
<td>de la Fuente &amp; Lostra 1994 [132]</td>
<td>BPD inpatients (n=20)</td>
<td>parallel, DB, PC</td>
<td>No significant positive effects</td>
</tr>
<tr>
<td>oxcarbazepin</td>
<td>Bellino et al 2005 [133]</td>
<td>BPD outpatients (n=17)</td>
<td>12-week, OL</td>
<td>Significant response to oxcarbazepine observed according to mean scores on the CGI-Severity, BPRS, and HRSA as well as items on the BPDSI</td>
</tr>
</tbody>
</table>
Pathologic Gambling

PG has traits in common with many different psychiatric disorders (see Fig. 3). The link between PG and antisocial disorders, including antisocial personality disorder (ASPD), conduct disorder, and adult antisocial behavior, is largely determined by genetic propensity. Slutske et al. [156] found that genetics accounts for 61 to 86% of the overlap between antisocial behaviors and PG and 16%-22% of variance for PG overall. Nonfamilial environmental factors also significantly contribute to PG, and to ASPD and adult antisocial behavior.

Antiepileptic Drugs for the Treatment of Impulsivity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Sample</th>
<th>Method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>topiramate</td>
<td>Nickel et al 2004 [134]</td>
<td>- females with BPD (n=29)</td>
<td>- 8-week, DB, PC</td>
<td>- topiramate showed significantly more efficacy than placebo based on measures of STAXI</td>
</tr>
<tr>
<td></td>
<td>Nickel et al 2005 [135]</td>
<td>- males with BPD (n=42)</td>
<td>- 8-week, DB, PC [135] with 18-month OL follow up [136]</td>
<td>- significant changes on STAXI scales observed</td>
</tr>
<tr>
<td></td>
<td>Nickel et al 2008 [136]</td>
<td></td>
<td></td>
<td>- topiramate group experienced a significantly greater change than placebo group on all STAXI scales upon follow up</td>
</tr>
<tr>
<td></td>
<td>Loew et al 2006 [137]</td>
<td>- females with BPD (n=56)</td>
<td>- 10-week, randomized, DB, PC</td>
<td>- treatment significantly improved global psychological stress (SCL-90) and healthy related quality of life (SF-36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- treatment reduced aggressive behavior, anxiety, phobic anxiety, insecurity in social contact, and somatization (SCL-90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- significant weight loss observed</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>Pinto &amp; Akiskal 1998 [141]</td>
<td>- BPD without concurrent MDD (n=8)</td>
<td>- OL</td>
<td>- 2 subjects were discontinued to do adverse events; of the remaining 6, 3 were robust responders with increase in overall level of functioning, cessation of impulsive behaviors,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- maintained response at 1-year follow up</td>
</tr>
<tr>
<td>Preston et al 2004 [140]</td>
<td>- bipolar disorder patients (n=35), subgroup of 40% meeting criteria for BPD</td>
<td>- retrospective</td>
<td>- 43% of those with BPD symptoms experienced a reduction in symptoms during treatment</td>
<td></td>
</tr>
<tr>
<td>Tritt et al 2005 [145]</td>
<td>- females with BPD (n=24)</td>
<td>- 8-week, randomized (2:1 ratio), DB, PC</td>
<td>- treatment group demonstrated changes on four STAXI scales (state-anger, trait-anger, anger-out, anger-control)</td>
<td></td>
</tr>
<tr>
<td>Weinstein &amp; Jamison 2007 [142]</td>
<td>- BPD patients with continuing symptoms of affective instability while taking medications (n=13)</td>
<td>- retrospective chart review</td>
<td>- patients had initial CGI-Severity scores or 5 or 6 and final scores of 1 or 2, except one patients with an initial score of 3 and a final score of 1 and one patient with an initial score of 6 and a final score of 7</td>
<td></td>
</tr>
<tr>
<td>Leiberich et al 2008 [146]</td>
<td>- females with BPD (n=27) from Tritt et al 2005 [145]</td>
<td>- 18-month, follow-up observation study, tested every 6 month</td>
<td>- lamotrigine group experienced greater changes on all STAXI scales compared to placebo group</td>
<td></td>
</tr>
<tr>
<td>gabapentin</td>
<td>Morana et al 2004 [152]</td>
<td>- Cluster B PD (n=28): antisocial (n=8), impulsive type (n=13), histrionic (n=7), narcissistic (n=1)</td>
<td>- 6-weeks, treated with maximal dose of gabapentin alone or with other drugs (neuroleptics, mood stabilizers, benzodiazepines)</td>
<td>- improvement in 23 (79.9%) of patients, with a decrease in aggressiveness, impulsivity, antisocial behavior, and drug abuse, and increase in concentration, introspection abilities, and interest in productive activities</td>
</tr>
<tr>
<td>Peris et al 2007 [153]</td>
<td>- BPD patients not responsive to previous therapy</td>
<td>- 6-month follow-up trial, OL</td>
<td>- global improvement, especially in anxious and depressive symptomology, was observed</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- no AEs reported</td>
<td>- studies of ICDs with AEDs are reviewed here (see Table 4), with a focus on PG in particular as an example of an ICD for which treatment with AEDs has shown some promise.</td>
</tr>
</tbody>
</table>

Notes: BPD=borderline personality disorder; OL=open-label; OAS-M=Overt Aggression Scale-Modified; SCL-90=Symptom Checklist 90; BPRS= Brief Psychiatric Rating Scale; PD=Personality Disorder; DB=double-blind; CGI=Clinical Global Impressions Scale; GAS=Global Assessment Scale; PD=personality disorder; IED=intermittent explosive disorder; PTSD=posttraumatic stress disorder; CO=Crossover; HRSA=Hamilton Rating Scale for Anxiety; BPDSP=Borderline Personality Disorder Severity Index; STAXI=State Trait Anger Expression Inventory; SF-36=Short Form 36 Health Survey; MDD=major depressive disorder; AEs=adverse events
Antisocial behavior is not just a consequence of PG, but 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 accordance, impulsivity can be thought of as a common endophenotype, or non-obvious underlying trait, in these and related psychiatric disorders.

An understanding of the neurobiology of PG is beginning to emerge. In functional magnetic resonance imaging studies, researchers observed that, compared with healthy subjects, pathological gamblers have decreased activity in their ventromedial PFC during presentation of gambling cues [157] and during a cognitive inhibition task (Stroop color-word) [158]. The ventromedial PFC is associated with decision-making [159], and its OFC plays a role in the processing of rewards during the expectancy and experiencing of monetary gains or losses [15,129,160,161]. In a recent imaging study of pathological gamblers (N=7), Hollander et al. [161] 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 gyrus (BA 24), putamen, and the OFC (BA 47 and 10).

Table 4. Trials of AEDs in Impulse Control Disorders

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Sample</th>
<th>Method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>topiramate</td>
<td>Shapira et al 2002</td>
<td>- PWS (n=3)</td>
<td>8-week, OL</td>
<td>attenuation of SIB with resultant lesion healing</td>
</tr>
<tr>
<td></td>
<td>[178]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shapira et al 2004</td>
<td>- PWS (n=8)</td>
<td>8-week, OL</td>
<td>improvement in self-injury (i.e., skin-picking)</td>
</tr>
<tr>
<td></td>
<td>[179]</td>
<td></td>
<td></td>
<td>No significant changes in calories consumed, BMI, or appetite</td>
</tr>
<tr>
<td></td>
<td>Dannon et al 2005</td>
<td>- male PGs (n=13)</td>
<td>12-week, randomized to topiramate or fluoxetine</td>
<td>9/12 topiramate completers reported full remission of gambling behavior, 3 had partial remission</td>
</tr>
<tr>
<td></td>
<td>[166]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Lochner et al 2006</td>
<td>- Trich (n=14)</td>
<td>16-week flexible dose followed by 2-4 week taper, O</td>
<td>- of 9 completers, severity of hair pulling decreased from baseline to endpoint</td>
</tr>
<tr>
<td></td>
<td>[180]</td>
<td></td>
<td></td>
<td>CGI-Improvement scores suggested no significant reduction in hair-pulling, but 6/9 were classified as responders</td>
</tr>
<tr>
<td></td>
<td>Dannon et al 2007</td>
<td>- PGs from previous studies who were full responders to a previous drug treatment regimen (n=43)</td>
<td>9-month (3-month OL followed by 6-month medication-free follow-up phase)</td>
<td>- most patients did not relapse during 6-month medication-free period</td>
</tr>
<tr>
<td></td>
<td>[175]</td>
<td></td>
<td></td>
<td>- 3/9 topiramate patients relapsed, but reported a decrease in gambling losses</td>
</tr>
<tr>
<td></td>
<td>Hollander et al, in prep</td>
<td>- PGs (n=42)</td>
<td>14-week, randomized, DB, P</td>
<td>topiramate was not effective in treating gambling symptoms or severity, but there were improvement trends on the BIS</td>
</tr>
<tr>
<td></td>
<td>[176]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>lamotrigine</td>
<td>Grant et al 2007</td>
<td>- pathologic skin picking patients (n=23)</td>
<td>12-week, OL</td>
<td>treatment associated with improvements in two thirds of subjects</td>
</tr>
<tr>
<td></td>
<td>[186]</td>
<td></td>
<td></td>
<td>mean time per day spent picking decreased significantly and 7 subjects (29.2%) reported no picking at endpoint</td>
</tr>
</tbody>
</table>

Notes: PWS=Prader-Willi Syndrome; SIB=self-injurious behavior; BMI=body mass index; PG=pathological gambler; Trich=trichotillomania; CGI=Clinical Global Impressions Scale; AE=adverse event; DB=double-blind; PC=placebo-controlled; OL=open-label; BIS=Barratt Impulsivity Scale; PG-YBOCS=Pathological Gambling Yale-Brown Obsessive-Compulsive Scale

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. Noradrenaline is associated with the arousal and risk taking in patients with PG. Dopamine is linked to positive and negative reward and the addictive component of PG [162]. Studies suggest that potentially useful treatments for PG include the SSRIs clomipramine [163] and fluvoxamine [164-166], the opioid antagonist naltrexone (may reduce the “high” associated with gambling) [167], the mood stabilizer lithium [168-170], and the anticonvulsants carbamazepine [171] and topiramate [166,172].

While SSRIs may be effective for some patients with PG [163-166], those with comorbid conditions, like bipolar
spectrum disorders, may relapse during treatment. Thus treatment with AEDs for PG has been suggested, especially when mood symptoms are present. Findings thus far suggest the efficacy of the AEDs valproate and topiramate in the treatment of PG. In the first controlled trial of the efficacy of mood stabilizers in PG, Pallanti et al. [169] evaluated the efficacy and safety of lithium and valproate in nonbipolar pathological gamblers. At the end of the 14-week trial, both the lithium and the valproate groups showed significant improvement in mean score on the Y-BOCS Modified for PG and did not significantly differ from each other on this improvement. Thirteen (68.4%) of the 19 patients taking valproate and 14 (60.9%) of the 23 patients taking lithium and were responders based on a Clinical Global Impressions-Improvement Scale (CGI-I) score of much or very much improved. However, this was a single-blind design with a small sample size and alcohol and substance abusers were excluded, yet both alcohol and substance use are highly comorbid with PG. A double-blind, placebo-controlled trial with a more representative sample, over a longer period of time is needed to support these initial findings.

PG may be characterized by two core, non-exclusive, and possibly synergistic neurobiological mechanisms, namely dysregulated craving/addiction proneness and mood/impulsivity. Topiramate may have an effect on the addictive aspect of PG by attenuating the release of dopamine in the mesolimbic circuit [173], which is thought to play a key role in behavior reinforcement and craving [174]. Dannon et al. [166] 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 3 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 8 fluvoxamine completers reported a full remission, and the remaining 2 fluvoxamine completers reported a partial remission. The fluvoxamine group showed a nonsignificant improvement in the CGI-I score at week 12. This evidence suggests that, although they have different mechanisms of action, both topiramate and fluvoxamine may help ameliorate PG symptoms.

Despite the randomized, blind-rater design, a major limitation of this study is the lack of a placebo control group. Thus, the improvement at 12 weeks in both groups may have been due to a high rate of placebo response. In addition, symptom remission was partially measured by patient self-reports, which can be subject to observer bias. Finally, these results may not be generalizable to the larger PG population as the sample was all male and patients with comorbid psychiatric diagnoses were excluded. Still, this study did show that topiramate was well tolerated with 12 of 15 topiramate subjects completing the study, the majority of which had a full remission. Further, in a naturalistic long-term follow-up study of 9 male pathological gamblers who responded to a 6-month trial of topiramate, most patients maintained full-response during a 6-month medication-free follow-up phase [175]. Three of the 9 patients relapsed.

Recently, Hollander (2008) [176] completed a randomized, 14 week, double-blind, placebo-controlled, multicenter trial of topiramate (flexibly dosed to 300 mg or the maximum tolerated dose) for the treatment of PG (N=42). Topiramate was not effective in treating gambling symptoms or severity, but there were improvement trends on the Barratt Impulsiveness Scale. Thus, perhaps topiramate should be investigated further as a treatment for impulsivity, a symptom of many ICDs including PG.

Other ICDs
Results from open-label studies and case reports suggest that topiramate may be effective for the treatment of a number of other ICDs, including kleptomania [177], skin-picking [178,179], trichotillomania [180], and IED [181,182]. In addi-
tion, topiramate augmentation of clomipramine/fluvoxamine was reported useful in a case of trichotillomania [183], and a patient with compulsive-impulsive sexual behaviors (and type II bipolar disorder) improved dramatically after three months’ addition of topiramate to citalopram [184].

Prader-Willi syndrome (PWS) is a multisystem neurogenetic obesity disorder with behavioral manifestations, including hyperphagia, compulsive behavior, mild to moderate mental retardation, and self-injurious behaviors (SIBs) in the form of skin picking, nail biting and rectal gouging. In the first published study of topiramate for the treatment (8 week, open-label) of PWS or SIB, Shapiro et al. [178] report attenuation of SIB resulting in lesion healing in three PWS adults treated with topiramate in an 8-week open-label trial. In another 8-week open-label study, Shapiro et al. [179] evaluated adjunctive therapy with topiramate in 8 adults with PWS. Topiramate did not significantly change compulsions, calories consumed, Body Mass Index, or increase self-reported appetite. However, there was a clinically significant improvement in the self-injury (i.e., skin-picking) characteristic of this syndrome. Double-blind placebo-controlled and cross-over studies are needed to establish the role of topiramate in attenuating SIB in PWS and other disorders involving SIB.

In an open-label pilot study, Lochner et al. [180] investigated the efficacy of topiramate in 14 adults with trichotillomania. Patients received 16 weeks of flexible dose treatment (50-250 mg/day), followed by a flexible dose taper over 2-4 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, 6 of 9 completers were classified as responders. Five patients dropped out due to adverse effects. These results suggest that topiramate may be useful in the treatment of trichotillomania, but more appropriately powered randomized placebo-controlled trials are needed.

Dannon [177] reported 3 kleptomanic patients who responded well to topiramate given either alone or in combination with SSRIs. Kaufman et al. [185] describe two patients with ICDs with aggressive features and post-encephalitic epilepsy where adjunctive tiagabine, an anticonvulsant novel GABA reuptake inhibitor, was effective in the management of both epilepsy and severe ICD with a marked decrease of impulsive and aggression behaviors. This makes sense since GABAergic modulation has been shown to be important in impulsive aggression.

In terms of other AEDs for ICDs, De Dios Perrino et al. [181] report 3 IED patients in which a good control of aggressive behavior was achieved using SSRIs and carbamazepine. In a survey completed by 2543 psychiatrists in the US in 1988, carbamazepine was reported to be moderately to markedly effective in 65.2% of IED, and 43.0% of BPD patients [182]. In a recent 12-week open-label trial, lamotrigine (25 mg every 2 days to 300 mg/day), a relatively new AED with mood-stabilizing properties, was associated with improvements in two thirds of subjects with pathologic skin picking (N=24) (based on DSM-IV criteria for other ICDs) [186]. Mean time per day spent picking decreased significantly and 7 subjects (29.2%) reported no picking at end-point. Further, dramatic improvement in compulsive-impulsive sexual behaviors was observed (which remained at 18 months follow-up) in a male who was started on lamotrigine in conjunction with fluoxetine for a chronic mixed mood disordered state [187].

In sum, these studies suggest that AEDs may be effective treatments for ICDs but double-blind placebo controlled studies are needed before any conclusions or recommendations can be made.

V. DISCUSSION

Effective treatment of impulsivity depends on determining the cause/causes of these behaviors and selecting treatments accordingly. Pharmacological treatments may reduce impulsivity 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 impulsive behavior, may be most effective for the long term treatment of the underlying chronic or recurrent illness [188]. 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 upon their symptom presentation. For example, BPD patients with prominent perceptual distortion may respond to neuroleptics, while those with depressed mood may respond best to antidepressants. Biological and behavioral dimensions may underlie treatment response in personality disordered patients [19,189]. There may be several developmental trajectories to impulsivity (e.g., ADHD, bipolar spectrum, trait impulsivity) and various routes to altering motivational circuitry, like modulating of cortico-striatal-limbic circuits. We suggest that core symptoms within disorders should be treated and appropriate outcome measures should be used to determine targeted treatment response.

Based on the evidence presented here, AEDs appear to be effective for treating the symptom domain of impulsivity 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 upon the comorbidity [147]. Thus, AEDs, traditionally used to treat bipolar disorder, can also be effective for ICDs and cluster B personality disorders, especially when bipolar symptoms are associated with the primary diagnosis or when there is an affective component to the primary
symptomology. When treating the core symptoms of impulsivity, the associated bipolar and mood lability symptoms may improve as well. So clinicians should treat target symptoms like impulsivity regardless of the 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 PG with a comorbid obsessive-compulsive spectrum disorder or OCD features, SSRI's may not be optimal treatment of PG with comorbid ADHD or bipolar spectrum disorders [190,191]. 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 [164]. Thus, a mood stabilizing AED like VPA may be a better treatment option for ICD patients with a comorbid bipolar disorder.

Accordingly, BPD patients with comorbid bipolar II or subclinical symptomology may benefit from mood stabilizing AEDs, like carbamazepine if irritability is pronounced [114]. Personality disorders with aggressive behavior, and emotionally unstable character disorder with mood swings, respond to AEDs. A variety of personality factors and comorbid conditions over-represented 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 be needed, or safer, but less effective drugs may need to replace more effective drugs whose abuse in suicidal patients may have dangerous consequences [148].

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

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