Intermittent Explosive Disorder At A Glance

Intermittent explosive disorder is characterized by repeated outbursts of aggressive, violent behavior. Persons with intermittent explosive disorder may attack others and destroy property. Between outbursts, they may express remorse, regret or embarrassment.

TREATMENT

Anecdotal reports, suggest that intermittent explosive disorder (IED) may be less responsive to insight-oriented psychotherapies and more responsive to cognitive-behavioral and addiction-based therapies, particularly those stressing anger management techniques.[1]

The following classes of medication may be useful for Intermittent Explosive Disorder:

Mood Stabilizers	Carbamazepine
Antiepileptics	Propranolol
Dopamine Antagonists	Fluoxetine
Beta Blockers	Amytriptiline
MAO-Inhibitors	Phenelzine
SSRIs	Tranylcypromine
Tricyclic Antidepressants	Trifluoperazine
Lithium	Olanzapine
Haloperidol	Desipramine
Valproate	

Non-pharmacological treatment centers on Cognitive-Behavioral interventions, particularly anger management. Dialectical-Behavioral Therapy also has been reported effective. Other forms of therapy, specifically insight-oriented therapy and relaxation therapy, have been found ineffective or have not yet been sufficiently studied.

There is no consensus about the duration of treatment, however, empirical evidence and experience suggest that treatment should be chronic and entails use of both medication and psychotherapy. It appears that some persons with this disorder benefit from multiple drugs from different classes.

Discussion

Classes of drugs reported to be effective in persons with probable or possible intermittent explosive disorder in controlled trials include mood stabilizers, antiepileptics, dopamine antagonists, and beta-blockers. In a single-blind, controlled study of lithium in impulsively violent prison inmates with personality disorders, 12 men were randomized

to 12-week trials of lithium-placebo-lithium or placebo-lithium-placebo (Sheard 1971). Subjects displayed significant reductions in violent incidents and self-assessment of angry affect and tension during the lithium periods compared with the placebo periods. In a 4-week double-blind, placebo-controlled study of lithium and haloperidol in 61 children ages 5–12 years with conduct disorder hospitalized for explosive aggression, both lithium and haloperidol were significantly superior to placebo in reducing measures of aggression, hyperactivity, and hostility (Campbell et al. 1984). A 6-week double-blind, placebo-controlled study of lithium in 50 children of the same age and diagnosis, again deemed lithium superior to placebo (Campbell et al. 1995).

In a double-blind, placebo-controlled crossover trial of valproate in 20 adolescents with disruptive behavior disorders who met specific diagnostic criteria for explosive temper and mood lability, subjects received 6 weeks of valproate followed by 6 weeks of placebo, or the reverse, by random assignment (Donovan et al. 2000). After the first 6 weeks, 8 (80%) of the 10 patients randomized to valproate responded compared with none of the 10 placebo-treated patients ($P < 0.001$, Fisher exact test, two-tailed). Of the 15 subjects who completed both 6-week treatment phases, 12 met response criteria only while receiving valproate, 1 only while receiving placebo, 1 while receiving both treatments, and 1 in neither phase ($P = 0.003$, sign test). In contrast, in a 12-week study of 246 patients with impulsive aggression, valproate was not superior to placebo in reducing aggression scores in the 116 subjects with broadly defined intermittent explosive disorder (Hollander et al. 2003).

A controlled comparison of carbamazepine and propranolol in 80 patients with rage outbursts attributed to a variety of diagnoses, including intermittent explosive disorder ($n = 51$) and attention-deficit disorder, residual type ($n = 38$) found the two drugs were equally beneficial in reducing rage outbursts (Mattes 1990). Although this study lacked a placebo group, the diagnosis of intermittent explosive disorder was associated with better response to carbamazepine, whereas the diagnosis of attention-deficit disorder was associated with better response to propranolol. In a placebo-controlled crossover study of two dosages of phenytoin (100 and 300 mg/day) administered for 4 weeks to 13 male inmates in a maximum-security prison with impulsive aggression defined as "spontaneous hair-trigger acts," phenytoin at 300 mg/day—but not placebo or phenytoin at 100 mg/day—significantly reduced the frequency of aggressive acts as well as ratings of tension–anxiety and depression–dejection, however anger-hostility scores were not reduced. (Barratt et al. 1991). In another double-blind, placebo-controlled crossover study of phenytoin (300 mg/day) in 60 inmates divided into two groups based on whether they committed primarily impulsive or premeditated aggressive acts while in prison, phenytoin significantly reduced impulsive but not premeditated aggressive acts (Barratt et al. 1997).

Other medications reported effective in probable or possible intermittent explosive disorder in case reports and case series include desipramine, clomipramine, sertraline, venlafaxine, ethosuximide, primidone, metoprolol, antiandrogens, and benzodiazepines (Andrulonis et al. 1980; Berlin and Meinecke 1981; Feder 1999; Mattes 1985, 1986; McElroy et al. 1998; Monroe 1975). Benzodiazepines have been reported useful when taken at low dosages or on an as-needed basis (Griffith 1985; Lion 1979). In addition, open-label studies suggest that antidepressants, particularly serotonin reuptake inhibitors,

may be effective for "anger attacks" in patients with depressive disorders and bipolar depression (Mammen et al. 2004), and placebo-controlled studies indicate that serotonin reuptake inhibitors, lithium, antipsychotics

Many medications have been used to treat impulsive aggression, such as tricyclic antidepressants, benzodiazepines, mood stabilizers, and neuroleptics. Pharmacotherapy studies of aggression have indentified SSRIs and mood stabilizers as first-line treatments. Fluoxetine and other SSRIs have been studied in impulsive aggressive subjects and IED patients. In a treatment trial of subjects meeting IED-IR criteria, impulsive aggressive behavior did respond to fluoxetine (Coccaro and Kavoussi 1997), but non-serotonin-specific antidepressants had little benefit for impulsive aggression and many side effects in treatment studies. Soloff et al. (1986a) found that affective symptoms improved with amitriptyline in some BPD and schizotypal personality disorder inpatients, but impulsivity and aggression worsened in a set of patients, perhaps due to the noradrenergic effects of tricyclic antidepressants (Links et al. 1990). Thus, clinicians should be cautious when using the new dual-action antidepressants in these persons.

Monoamine oxidase inhibitors such as tranylcypromine and phenelzine have also been studied in impulsively aggressive subjects. In a double-blind study, Soloff et al. (1993) found that compared with placebo and haloperidol, phenelzine produced a moderate reduction in anger and hostility in BPD patients. Yet a 16-week continuation phase revealed that the subjects had experienced only minor benefits in depression and irritability and remained substantially impaired after the treatment phase (Cornelius et al. 1993; Soloff et al. 1993). In a double-blind crossover trial (Cowdry and Gardner 1988), treatment-resistant BPD patients with a history of impulsive aggression showed improvement with tranylcypromine, carbamazepine (decreased severity of behavioral dyscontrol), and trifluoperazine but had an increase in the severity and frequency of the episodes of serious dyscontrol with alprazolam. Benzodiazepine treatment might have released the subjects' control or inhibition of these episodes.

Mood stabilizers have also been used to treat aggression. Links et al. (1990) found objective ratings of anger and suicidality in BPD outpatients improved the most on lithium compared with desipramine and placebo, but subjects and their clinicians did not report any improvement in mood. Sheard et al. (1976) found an improvement using lithium versus placebo in chronically aggressive prisoners. Again, however, only objective findings supported this; no improvement was reported subjectively. Barratt et al. (1997) also reported a reduction in aggression with phenytoin in impulsive aggressive prisoners.

The other mood stabilizers studied for impulsive aggression are carbamazepine and divalproex. In the Cowdry and Gardner (1988) study, carbamazepine lessened episodes of impulsive aggression in BPD subjects, but 18% of subjects had a worsening of mood that improved once carbamazepine was stopped. Kavoussi and Coccaro (1998) and Hollander et al. (2003) reported an anti-aggressive effect of divalproex sodium in IED subjects with a Cluster B personality disorder. Given the relative adverse event profiles for SSRIs versus mood stabilizers, it is likely that clinical treatment of persons with IED should start with SSRIs unless the subject is extremely aggressive or has a

history of a bipolar disorder, in which case treatment with a mood stabilizer would be more appropriate.

The neuroleptics haloperidol, trifluoperazine, and depot flupenthixol have all been studied in BPD patients. Cowdry and Gardner's (1988) subjects showed significant improvement in depression and anxiety objective ratings with trifluoperazine, but subjective ratings did not support this. Trifluoperazine was seen as less useful than tranylcypromine (a monoamine oxidase inhibitor) and carbamazepine in improving behavior and affect among subjects. Soloff et al. (1986b), (1989) found that BPD inpatients improved on hostility and global function measurements with haloperidol, but considerable depression remained. Montgomery and Montgomery (1982) found that suicidal and parasuicidal behavior, in subjects with a history of such behaviors, decreased in a depot flupenthixol treatment group versus a placebo group. Zanarini and Frankenburg (2001) compared the atypical antipsychotic olanzapine with placebo in outpatients with BPD. The treatment improved anger, hostility, and other symptoms but did not improve depression, and patients remained quite ill.[2]

Psychotherapy

Therapy for anger and aggression is largely cognitive-behavioral group therapy. Imaginal exposure therapy, often used for anxiety disorders, was studied in an uncontrolled pilot study of anger treatment (Grodnitzky and Tafrate 2000). Subjects habituated to anger-provoking scenarios and the treatment was considered beneficial.

In a controlled trial of college students with high levels of driving anger, Deffenbacher et al. (2000) compared pure relaxation training with relaxation training combined with cognitive therapy and an assessment-only control. Neither treatment condition improved general trait anger, but both treatments improved driving anger. When repeated in a new population of drivers with higher anger levels, both treatments lowered trait anger (Deffenbacher et al. 2002). Because relaxation training with cognitive therapy provided little gain over pure relaxation training, relaxation training alone may be adequate treatment for driving anger.

Other versions of cognitive-behavioral therapy (CBT), such as dialectical behavior therapy, have been studied. One study found improvement in anger, social adjustment, and global functioning compared with a treatment-as-usual condition (Linehan et al. 1994). Improvement in anger and impulsivity has been shown with dialectical behavior therapy across many disorders. There are no published double-blind, placebo-controlled studies on IED subjects in therapy, but studies of therapy for IED subjects are ongoing.[3]

References

1. (Gabbard's Treatments of Psychiatric Disorders, 4th Edition, Glen O. Gabbard, M.D., Editor-in-Chief)-specific reference=Maletzky B: The episodic dyscontrol syndrome. Diseases of the System 341:Nervous 178–185, 1973

2. (The American Psychiatric Publishing Textbook of Psychiatry, 5th Edition Edited by Robert E. Hales, M.D., M.B.A., Stuart C. Yudofsky, M.D., and Glen O. Gabbard, M.D.)

3. (The American Psychiatric Publishing Textbook of Psychiatry, 5th Edition Edited by Robert E. Hales, M.D., M.B.A., Stuart C. Yudofsky, M.D., and Glen O. Gabbard, M.D.)

Additional Reading

Sheard MH: Effects of lithium in human aggression. Nature 230:113–114, 1971 [PubMed]

Campbell M, Small AM, Green WH, et al: Behavioral efficacy of haloperidol and lithium carbonate: a comparison in hospitalized aggressive children with conduct disorder. Arch Gen Psychiatry 41:650–656, 1984 [PubMed]

Campbell M, Adams PB, Small AM, et al: Lithium in hospitalized aggressive children with conduct disorder: a double-blind and placebo controlled study. J Am Acad Child Adolesc Psychiatry 34:445–453, 1995 [PubMed]

Donovan SJ, Stewart JW, Nunes EW, et al: Divalproex treatment for youth with explosive temper and mood lability: a double-blind, placebo-controlled, crossover design. Am J Psychiatry 157:818–820, 2000 [Full Text] [PubMed]

Hollander E, Tracy KA, Swann AC, et al: Divalproex in the treatment of impulsive aggression: efficacy in Cluster B personality disorders. Neuropsychopharmacol 28:1186–1197, 2003 [PubMed]

Mattes JA: Comparative effectiveness of carbamazepine and propranolol for rage outbursts. J Neuropsychiatry Clin Neurosci 21:249–255, 1990

Barratt ES, Kent TA, Bryant SG, et al: A controlled trial of phenytoin in impulsive aggression (letter). J Clin Psychopharmacol 11:338–339, 1991

Barratt ES, Stanford MS, Felthous AR, et al: The effects of phenytoin on impulsive and premeditated aggression: a controlled study. J Clin Psychopharmacol 17:341–349, 1997 [PubMed]

Andrulonis PA, Donnelly J, Glueck BC, et al: Preliminary data on ethosuximide and the episodic dyscontrol syndrome. Am J Psychiatry 137:1455–1456, 1980 [PubMed]

Berlin FS, Meinecke CF: Treatment of sex offenders with antiandrogen medication: conceptualization, review of treatment modalities, and preliminary findings. Am J Psychiatry 138:601–607, 1981 [PubMed]

Feder R: Treatment of intermittent explosive disorder with sertraline in 3 patients. J Clin Psychiatry 60:195–196, 1999 [PubMed]

Mattes JA: Metoprolol for intermittent explosive disorder. Am J Psychiatry 142:1108–1109, 1985 [PubMed]

Mattes JA: Psychopharmacology of temper outbursts: a review. J Nerv Ment Dis 174:464–470, 1986 [PubMed]

McElroy SL, Soutullo CA, Beckman DA, et al: DSM-IV intermittent explosive disorder: a report of 27 cases. J Clin Psychiatry 59:203–210, 1998 [PubMed]

Monroe RR: Anticonvulsants in the treatment of aggression. J Nerv Ment Dis 160:119–126, 1975 [PubMed]

Griffith JL: Treatment of episodic behavioral disorders with rapidly absorbed benzodiazepines. J Nerv Ment Dis 173:312–315, 1985 [PubMed]

Lion JR: Benzodiazepines in the treatment of aggressive patients. J Clin Psychiatry 40:70–71, 1979 [PubMed]

Mammen OK, Pilkonis PA, Chengappa KN, et al: Anger attacks in bipolar depression: predictors and response to citalopram added to mood stabilizers. J Clin Psychiatry 65:627–633, 2004 [PubMed]

Coccaro EF, Kavoussi RJ: Fluoxetine and impulsive aggressive behavior in personality disordered subjects. Arch Gen Psychiatry 54:1081–1088, 1997 [PubMed]

Soloff PH, George A, Nathan RS, et al: Paradoxical effects of amitriptyline in borderline patients. Am J Psychiatry 143:1603–1605, 1986a

Links PS, Steiner M, Boiago I, et al: Lithium therapy for borderline patients: preliminary findings. J Personal Disord 4:173–181, 1990

Soloff PH, Cornelius J, Anselm G, et al: Efficacy of phenelzine and haloperidol in borderline personality disorder. Arch Gen Psychiatry 50:377–385, 1993 [PubMed]

Cornelius JR, Soloff P, Perel JM, et al: Continuation pharmacotherapy of borderline personality disorder with haloperidol and phenelzine. Arch Gen Psychiatry 150:1843–1848, 1993 [Full Text] [PubMed]

Cowdry RW, Gardner DL: Pharmacotherapy of borderline personality disorder: alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. Arch Gen Psychiatry 45:111–119, 1988 [PubMed]

Sheard M, Manini J, Bridges C, et al: The effect of lithium on impulsive aggressive behavior in man. Am J Psychiatry 133:1409–1413, 1976 [PubMed]

Barratt ES, Stanford MS, Felthous AR, et al: The effects of phenytoin on impulsive and premeditated aggression: a controlled study. J Clin Psychopharmacol 17:341–349, 1997 [PubMed]

Kavoussi RK, Coccaro EF: Divalproex sodium for impulsive aggressive behavior in patients with personality disorder. J Clin Psychiatry 59:676–680, 1998 [PubMed]

Hollander E, Tracy KA, Swann AC, et al: Divalproex in the treatment of impulsive aggression: efficacy in cluster B personality disorders. Neuropsychopharmacology 28:1186–1197, 2003 [PubMed]

Soloff PH, George A, Nathan RS, et al: Progress in pharmacotherapy of borderline disorders. Arch Gen Psychiatry 43:691–697, 1986b

Soloff PH, George A, Nathan RS, et al: Amitriptyline versus haloperidol in borderlines: final outcomes and predictors of response. J Clin Psychopharmacol 9:238–246, 1989 [PubMed]

Montgomery SA, Montgomery D: Pharmacological prevention of suicidal behavior. J Affect Disord 4:291–298, 1982 [PubMed]

Zanarini MC, Frankenburg FR: Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. J Clin Psychiatry 62:849–854, 2001 [PubMed]

Grodnitzky GR, Tafrate RC: Imaginal exposure for anger reduction in adult outpatients: a pilot study. J Behav Ther Exp Psychiatry 31:259–279, 2000 [PubMed]

Deffenbacher JL, Lynch RS, Oetting ER, et al: Characteristics and treatment of high-anger drivers. J Couns Psychol 47:5–17, 2000

Deffenbacher JL, Filetti LB, Lynch RS, et al: Cognitive-behavioral treatment of high anger drivers. Behav Res Ther 40:895–910, 2002 [PubMed]

Linehan MM, Tutek DA, Heard HL, et al: Interpersonal outcome of cognitive behavioral treatment for chronically suicidal borderline patients. Am J Psychiatry 151:1771–1776, 1994 [Full Text] [PubMed]