Subject Review

Therapeutic Use of Propranolol for Intermittent Explosive Disorder

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Intermittent explosive disorder is a syndrome characterized by episodic sudden outbursts of verbal abuse and physical violence in response to minor provocations. Propranolol has been proposed as a promising treatment for this cause of violent behavior. Of eight Mayo Clinic patients with intermittent explosive disorder who had been treated with propranolol between 1983 and 1985, five had substantial diminution or complete remission of symptoms. This response confirms the previously published reports of the effectiveness of propranolol in the treatment of intermittent explosive disorder.

Working with belligerent patients is a therapeutic challenge for many specialty fields in medicine. Psychiatrists, neurologists, and rehabilitation specialists often encounter patients with a variety of organic brain syndromes that are manifested by argumentative and violent behavior. Often the behavior of these patients stymies attempts at adequate medical care or social rehabilitation. Many such patients become institutionalized when families are unable to tolerate their rages at home.

Elliott[1] reviewed the episodic dyscontrol syndrome and described a group of patients with sudden, frequent outbursts of verbal or physical violence. These patients had an otherwise pleasant background personality and expressed sincere remorse for their behavior. Between episodes they were cooperative. Periodically, they would exhibit rage with a verbal or physical display of violence out of proportion to the provoking situation. Elliott noted that the type of violence manifested by such patients is unplanned and primitive (for example, biting, kicking, or shouting). He also found that most of these patients had some type of organic brain syndrome that caused or contributed to their lack of self-control.

Intermittent explosive disorder is the DSM-III (Diagnostic & Statistical Manual, third edition, of the American Psychiatric Association) diagnosis that most resembles Elliott's description of "episodic dyscontrol."[2] It is a disorder of impulse control, and the diagnostic criteria are as follows: (1) repeated discrete episodes of loss of control of aggression leading to physical assault or destruction of property, (2) behavior disproportionate to the triggering event, (3) absence of general impulsivity between episodes, and (4) exclusion of patients with schizophrenia, antisocial personality disorder, or conduct disorder. These criteria do not exclude patients with chemical addictions or patients with other organic brain syndromes.

Under the proposed draft of DSM-III-R (a revision of the third edition), this diagnostic category may be eliminated. Instead, many patients with episodic outbursts of violence will fulfill the criteria for "organic personality disorder—explosive type." This disorder is typified by episodic aggressive outbursts out of proportion to the triggering event in patients who have evidence of an abnormality in brain function or structure from the

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history, physical examination, laboratory studies, or neuropsychologic tests.[3]

Recently, several reports in the literature have advocated the use of propranolol for treatment of intermittent explosive disorder.[4-9] In this report, we review the clinical manifestations of intermittent explosive disorder, the current literature on the use of propranolol in patients with this disorder, and the experience with this treatment in the Department of Psychiatry and Psychology at our institution.*

DIAGNOSIS OF INTERMITTENT EXPLOSIVE DISORDER

Violent behavior is a complex biopsychosocial phenomenon. The patient who is undergoing assessment because of a complaint of violent behavior may or may not need medical or psychiatric intervention. Nevertheless, patients in whom the pattern of violence resembles the repetitive, unpredictable, erratic, and primitive pattern of episodic dyscontrol or intermittent explosive disorder merit careful evaluation. Many of these patients can be helped to control their behavior.

Several large series of patients with episodic dyscontrol have been published.[1,13-16] Although these studies were based on selected patient samples (for example, patients referred to neuropsychiatric clinics[14,16]), some generalizations can be made about the clinical evaluation of the patient with suspected intermittent explosive disorder.

The frequency, duration, and intensity of violent episodes should be documented. Because some patients have little recall for these episodes,[13] a collaborative history from family members or associates may be necessary. Whether a patient is only verbally abusive, directs rages against property or family members, or is indiscriminately violent can provide clues about the presence of psychodynamic factors, poor impulse control, or the need for inpatient versus outpatient evaluation. The onset of violent behaviors should be noted and may provide evidence for a possible biologic diathesis (as in posttraumatic personality change) or for genetic or environmental influences (when the behavior begins in childhood).

Pertinent information to elicit includes a history of possible abuse or neglect during childhood, a family pattern of violent behavior, and a personal history of impulsive actions such as reckless or aggressive driving, gambling, impulsive sexual activity, and risk-taking sports or recreational activities. Some patients have a history of criminal arrests, frequent moves or job changes, and chaotic family relationships. The type and duration of military service, educational background, need for special assistance in school, and possession of weapons or martial arts training may assist in formulating a diagnosis and treatment plan.

Relevant past medical history should include any type of metabolic or traumatic insult to the brain; if known, details of birth, delivery, and early childhood should be recorded. Any history of loss of consciousness, seizures, or pugilistic sports may help substantiate a suspected organic component. Eliciting a history of use of chemicals including alcohol, illicit drugs, and prescribed psychoactive agents is crucial to appropriate management. A family history of seizure disorder, substance abuse, psychiatric disease, or central nervous system disease should be sought.

Elliott,[14] Bach-Y-Rita and associates,[15] and Mungas[16] all stressed the frequent incidence of minimal brain dysfunction in patients with intermittent explosive disorder. Evaluation should include examination for neurologic "soft signs" and neuropsychiatric testing, if indicated. Such tests may provide supportive evidence for an attention deficit disorder, a treatable type of minimal brain dysfunction.

Seizure disorders have also been detected frequently in patients with intermittent explosive disorder.[1,16] The relationship of temporal lobe epilepsy to violent behaviors has long been noted and remains controversial. Certainly, an electroencephalogram should be obtained as an adjunct to clinical evaluation, when indicated. A normal electroencephalographic tracing does not, of course, exclude the possibility of seizure activity or of resolution of the patient's target symptoms with anticonvulsant treatment.[13]

Substance abuse is a frequent contributing factor in episodic dyscontrol. Bach-Y-Rita and associates[15] noted use of alcohol as a directly associated factor in 72 of 130 patients with this disorder. The specific syndrome of pathologic intoxication is characterized by violent outbursts

*For a discussion of other psychiatric effects and uses of propranolol, readers are referred to the reviews by Atsmon and Blum,[10] Johnson,[11] and Paykel and associates.[12]

associated with relatively little consumption of alcohol. Patients with personality disorders or organic brain syndrome predisposing to impulsive action may become aggressive under the disinhibiting influence of alcohol. Mungas[16] reported an association between alcohol and the severity of violent outbursts. Elliott[17] and Gunn[18] emphasized the need for abstinence in these patients. Certain substances such as phencyclidine and amphetamines are known to induce violent behaviors in some intoxicated persons.

A partial listing of conditions that have been associated with intermittent explosive disorder is shown in Table 1.[1,13-18] A screening laboratory examination might include a blood chemistry group (with fasting blood glucose, liver function tests, and electrolytes), electroencephalography, computed tomography, thyroid function test, syphilis serology, urinalysis, and urine drug-abuse survey. Depending on the clinical indications, more specialized testing such as cerebrospinal fluid examination, heavy-metal screen, glucose tolerance test, or androgenous hormone determinations might be pursued.

Psychiatric consultation should be sought if psychiatric disease is suspected or if the patient has suggestive evidence of maladaptive personality traits. Mungas[16] pointed out the high incidence of psychopathologic conditions in violent patients, including affective disorder, anxiety disorder, disorder of impulse control, and antisocial personality. Other personality disorders may predispose to intermittent explosive disorder, including borderline, narcissistic, and paranoid types.

Table 1.—**Some Findings Associated With Intermittent Explosive Disorder**

Minimal brain dysfunction (attention deficit disorder)
Seizure disorders
Temporal lobe epilepsy
Complex partial seizures
Substance use or abuse disorders (pathologic intoxication syndrome)
Head trauma (closed-head injury)
Hypoxic events
Metabolic disturbances
Hypoglycemia
Wilson's disease (hepatolenticular degeneration)
Hyperammonemia
Cushing's syndrome
Hormonal disturbances
Premenstrual tension syndrome
Hyperandrogenemia
Other diseases of the central nervous system
Dementias
Focal lesions (tumor, stroke, multiple sclerosis)
Increased intracranial pressure
Encephalopathies
Psychosocial factors
Family history of abuse or neglect
Chaotic childhood
Psychopathologic conditions
Affective disease
Psychotic disease
Personality disorders

TREATMENT OF INTERMITTENT EXPLOSIVE DISORDER

The initial approach in patients with intermittent explosive disorder should be specific therapy for any underlying medical or psychiatric condition. For many patients, however, even when a specific organic diagnosis can be made, no specific treatment is available (for example, patients with minimal brain dysfunction or Alzheimer's dementia). For these patients, several psychopharmacologic approaches have been tried.*

The major tranquilizers, especially the more sedating, less potent agents, often become the mainstay of pharmacologic treatment for patients with intermittent explosive disorder. There is growing concern, however, about long-term use of these agents when they are not clearly indicated by the presence of a thought disorder. The risk of movement disorders and anticholinergic side effects can be prohibitive in some patients.

The use of lithium in intermittent explosive disorder is supported by several published studies.[22-24] Recently, a growing body of literature has advocated the use of carbamazepine in mood disorders and intermittent explosive disorder as well.[25-28] Phenytoin is known to be effective in some patients, even in the absence of an apparent seizure disorder.[13,29] Ethosuximide has also been proposed as a possible treatment.[30]

Lion[31] and Griffith[32] have advocated the use of benzodiazepines in the treatment of intermittent explosive disorder. These agents, however, may produce a paradoxic excitement or disinhibiting effect in some patients.[20] Use of these agents is problematic among patients with substance abuse or dependency syndromes, because of their addictive potential.

*For more detailed reports, the reader is referred to the reviews by Rickler,[19] Sheard,[20] Gunn,[18] and Lion.[21]

Stimulant drugs (for example, methylphenidate) can benefit those patients for whom attention deficit disorder is a known or suspected contributing factor.[33]

Psychotherapeutic approaches to intermittent explosive disorder are legion. Classic behavioral conditioning programs may be implemented in institutional settings and may provide relief from violent disruption of an entire ward. Individual or group counseling may enable patients to identify potentially provoking situations and learn to avoid them. A self-imposed "time-out" to regain self-control and thereby enhance self-esteem may be effective. Insight-oriented psychotherapy is indicated for those patients in whom internal conflicts lead to repetitious acting-out. Conjoint marital or family therapy may be necessary to interrupt family systems of aggressor and victim roles.

Finally, psychosurgical techniques have been useful for carefully selected persons whose behavior is otherwise uncontrollable.[17,34,35]

Unfortunately, the available therapeutic armamentarium is not definitive for all patients. Therefore, careful consideration of the use of any promising new agent for the treatment of intermittent explosive disorder is prudent.

REVIEW OF REPORTS IN THE LITERATURE

Elliott[4] first reported the use of propranolol in intermittent explosive disorder in an account of seven adult patients in 1977. All his patients had some type of acute, traumatic brain damage. Target symptoms included belligerence, explosive outbursts, and general irritability that had been present for periods that ranged from 2 weeks to 9 months. In all patients, remission or control of target symptoms was achieved by using propranolol in dosages of 60 to 240 mg/day. In three patients, discontinuation of the propranolol therapy did not result in recurrence of symptoms.

In contrast to Elliott's adult patients with acute head injury, Schreier[36] reported the case of a 12-year-old boy who was recovering from viral encephalitis. Treatment with 100 mg of propranolol daily led to remission of agitated, belligerent behavior and hallucinations.

In 1981, several additional cases of intermittent explosive disorder were reported. Those described by Yudofsky and colleagues[5] included a wide variety of organic diagnoses such as childhood anoxia, Wilson's disease (hepatolenticular degeneration), head injury, and mental retardation. These investigators used high dosages of propranolol—320 to 520 mg/day. In one patient (a woman with Wilson's disease), propranolol seemed to control seizures as well as target symptoms of assaults and property destruction; her psychosis was unaffected.

Petrie and Ban[37] used propranolol to control the agitation of three patients (54, 71, and 86 years old) with senile and presenile dementia. At dosages of 60 to 160 mg/day, propranolol treatment controlled wandering and destructive behaviors and in one patient was associated with substantial improvement of mental status.

Mansheim[38] reported a case of a 32-year-old woman whose target symptoms of assaultive and self-destructive behaviors had been present since she was involved in a car accident at age 16 years. She also sustained a left hemiparesis and had moderate mental retardation. Aggressive symptoms were controlled with 60 mg of propranolol daily. Ratey and associates[6] described three patients with intermittent explosive disorder, including one with schizophrenia. Verbal and physical assaults subsided after administration of 200 mg of propranolol daily, but the patient's thought disorder remained unchanged and she continued to require neuroleptic treatment. Most recently, Yudofsky and colleagues[7] reported a case of extremely violent behavior in a 40-year-old man with Korsakoff's psychosis controlled by propranolol (600 mg/day). This propranolol therapy allowed removal of physical restraints, which had been required previously.

Williams and associates[8] published the first large series of patients with violent behavior. In this retrospective review, the 30 patients (26 male and 4 female patients) ranged in age from 7 to 35 years. The psychiatric diagnoses were conduct disorder, 25 (including 22 patients with attention deficit disorder); intermittent explosive disorder, 3; and pervasive developmental disorder, 2. All patients had neurologic diagnoses as well: uncontrolled seizures in 11, controlled seizures in 3, "possible" seizures in 4, focal neurologic deficit in 9, and minimal brain dysfunction in 9.

In this group of patients,[8] propranolol was given in a starting dosage of 30 to 80 mg/day; every third day, the dose was increased by 30 to 80 mg. If the pulse was 50 beats/min or less or the blood

pressure was less than 80/50 mm Hg, the dose was not administered. The final dosages ranged from 50 to 1,600 mg/day, the end point being either clinical change in behavior or limiting side effects of β-blockade. The effective dosage range, however, was smaller—from 50 to 950 mg/day (mean, 160 mg/day). The results in this study were encouraging: 75% of patients were thought to have an improved condition. Of those with improvement, several were able to discontinue the use of other medications and take only propranolol. The outcome was unrelated to age, sex, intelligence, neurologic or psychiatric diagnosis, current medication, or inpatient or outpatient status.

Greendyke and associates[9] reported a smaller but valuable study of eight patients with intermittent explosive disorder. In this nonrandomized, nonblinded, prospective study, each patient served as his own control during 80 days of baseline observation. Nurses, family members, and physicians were involved in evaluating change in the behavior of these patients. The authors' attempt at quantifying their data is hampered by the small series, but they chose a measurable end point of number of assaults per 20-day observation period. All subjects were male inpatients at a Veterans Administration hospital who had severe neurologic or behavioral impairment and ranged in age from 44 to 79 years. Six patients received neuroleptics concomitantly with propranolol. The authors increased the dose of propranolol every 3 to 5 days until no further clinical improvement was seen or limiting side effects were encountered (generally at 520 mg/day). This dosage was maintained for an 80-day observation period.

All but one of the eight patients showed diminished aggressive behavior. In six patients, the number of physical assaults decreased from seven to one per 20 days. The one patient with no improvement was sensitive to side effects, which limited his dosage to 200 mg/day. The authors thought that this dose was inadequate to evaluate a potential response to propranolol. They also strongly believed that target symptoms needed as long as 4 weeks to respond to propranolol, an opinion consistent with that of many other investigators but in contrast to some reports in which improvement has been noted within days after initiation of treatment in adequate doses.

Mattes and colleagues[39] published preliminary results of a prospective study in which propranolol was compared with carbamazepine for treatment of intermittent explosive disorder. They indicated that both drugs seemed to be effective, but because of side effects, propranolol was used in only 7 patients and carbamazepine in 21. No data about selection of patients, dose, or method of rating the observed behavior were reported.

Roach and associates[40] published a case report of a 32-year-old man without diagnosed central nervous system disease in whom propranolol relieved symptoms of "uncontrollable rage and anger," which had been present since adolescence. Their patient received only 60 mg of propranolol daily and concurrent psychotherapy.

Recently, Mattes[41] also described two patients in whom metoprolol was useful for controlling violent behavior when propranolol could not be tolerated.

In another recent publication, Greendyke and co-workers[42] reported a double-blind, crossover, placebo-controlled study of nine men with organic brain syndrome that resulted in dementia. With use of dosages of 520 mg/day for 11 weeks, they demonstrated significantly fewer assaults while patients received propranolol. The overall results were rated as marked improvement in five patients, moderate improvement in two, and little change in two.

All studies of intermittent explosive disorder are hampered by the lack of objective criteria for aggressive behaviors and by the relative infrequency of the behaviors being studied. For rigorous comparison of behavior across time or populations, some quantifiable measure should be used. Observation periods must be sufficiently long to demonstrate change in behavior. Descriptions of violent behavior are occasionally useful, but such records can be subjectively written and read. Behavior that constitutes intolerable "verbal aggression" or "physical destruction" at one institution may be unremarkable elsewhere, depending on patient populations and ward policies. Yudofsky and associates[43] recently published the Overt Aggression Scale, which may benefit future studies.

Further confusion stems from the need for diagnostic labels in a problem that is multifactorial. Although "episodic dyscontrol syndrome" and "intermittent explosive disorder" are useful concepts, they lack precise definition and impart no information about social setting, severity of violent behaviors, or possible cause.

REPORT OF MAYO CLINIC CASES

We identified eight patients who had been treated with propranolol for intermittent explosive disorder by various psychiatrists at our institution between 1983 and 1985. This group consisted of five male and three female patients who ranged in age from 14 to 50 years. The propranolol dosages were 80 to 300 mg/day. In the judgment of the treating physicians, two patients had complete remission of target symptoms, three had substantial improvement, two had questionable improvement, and one had worsening of the disorder. The case descriptions are summarized in Table 2.

Case 1.—A 19-year-old man with a 2-year history of poorly controlled paranoid schizophrenia was admitted to an adolescent psychiatric unit after 8 months of unmanageable behavior. The patient also had borderline mental retardation (Wechsler Adult Intelligence Scale—Revised Full-Scale IQ = 85) and a mildly elevated serum creatinine concentration due to old pyelonephritis.

The psychotic thought disorder responded to thiothixene (45 mg/day), and benztropine (2 mg/day) was added to control dystonic reactions. The patient continued to have sudden, brief outbursts of shouting or physical threatening in response to relatively trivial frustrations (for example, a delay in receiving a weekly allowance or verbal teasing by other adolescents). During these outbursts, the patient would chase or strike at other patients and on one occasion put his hands around a staff member's throat. He was ashamed of these episodes and worked at cooperating by participating in a behavioral modification program. Propranolol therapy was begun at 40 mg/day and increased over 3 weeks to 100 mg/day. All outbursts ceased within 5 days after reaching the dosage of 100 mg/day. After 10 days of observation on this regimen, it was discontinued, and the violent outbursts recurred within 3 days. Administration of propranolol was reinstituted (80 mg/day), and striking improvement in behavior was again noted. The patient was dismissed on the following regimen: propranolol (80 mg/day), thiothixene (35 mg/day), and benztropine (2 mg/day). At 6 months, telephone contact with the patient's mother indicated that he was doing well at a rehabilitation school that had previously expelled him for his violent behavior.

Case 2.—A 21-year-old man was hospitalized in a physical medicine and rehabilitation unit after sustain-

Table 2.—**Summary of Mayo Clinic Patients With Intermittent Explosive Disorder Who Were Treated With Propranolol**

Case	Age (yr) and sex	Diagnosis	Target symptoms	Propranolol therapy: Duration (yr) of symptoms before	Propranolol therapy: Dose (mg/day)	Other medications	Response
1	17 M	Paranoid schizophrenia, mild mental retardation, old pyelonephritis	Sudden outbursts of verbal and physical aggression	2/3	80-100	Thiothixene, benztropine	Complete remission
2	21 M	Closed-head injury	Agitation, aggression	6 wk	240	Chlordiazepoxide, thiothixene	Complete remission
3	50 F	Profound mental retardation, tardive dyskinesia	Negativism, screaming, striking out	50	90	Thioridazine	Substantial improvement
4	14 M	Spina bifida and meningomyelocele	Impulsive, angry outbursts 1-5x/day	1/2	90	...	Substantial improvement
5	20 F	Encephalitis at age 2, skull fracture at age 3, mild mental retardation, impulse control disorder, seizures	Screaming tantrums, irritability, negativistic verbal and physical outbursts	17	300	Carbamazepine, primidone, acetazolamide	Substantial improvement
6	33 F	History of ruptured aneurysm, subarachnoid hemorrhage, hydrocephaly, encephalopathy	Physical aggression, "unmanageable" violent outbursts	3	200	Thioridazine (as needed)	Partial improvement of target symptoms only
7	16 M	Mild mental retardation, seizure disorder, congenital hemihypertrophy of left leg, history of PDA and ASD*	Agitation, angry outbursts of verbal and physical aggression	14	300	Valproic acid	Unimproved
8	48 M	Degenerative brain disease of unknown cause, seizures, dementia	Striking out, throwing furniture, yelling	1	80	Diazepam, valproic acid	Worse (increased agitation)

*ASD = atrial septal defect; PDA = patent ductus arteriosus.

ing a closed-head injury in a motor vehicle accident. As he emerged from a coma, he was belligerent and combative, and although his neurologic status rapidly improved, he continued to be agitated and aggressive with the hospital staff. A psychiatric consultation was obtained, but neuroleptics and benzodiazepines failed to control the patient's behavior during 5 weeks at therapeutic doses.

The patient was transferred to a closed psychiatric unit, and treatment with propranolol was initiated. The dosage was slowly increased to 240 mg/day. He became cooperative and pleasant, and after 5 days of receiving this daily dose, he was able to return to the rehabilitation unit and continue treatment there. The dosages of chlorpromazine and thiothixene were tapered and then discontinued, and only propranolol was administered. After 4 weeks, use of propranolol was also discontinued because of the occurrence of bradycardia. The aggressive behaviors did not recur during 5 months of follow-up.

Case 3.—A 50-year-old woman had had profound mental retardation since birth and had been institutionalized almost all her life. The records indicated that the patient had been restless and undisciplined as a child. She was negativistic and frequently screamed, destroyed property, and struck the staff. Over the years, many medications had been used, but the patient's behavior seemed responsive only to thioridazine. A severe tardive dyskinesia developed in 1975, but as the patient's difficult behavior escalated, her thioridazine dosage was slowly increased to 600 mg/day. In 1984, treatment with propranolol (90 mg/day) was begun, after which the staff reported better motivation, cooperation, and self-care. The dosage of thioridazine was decreased over the next few months to 350 mg/day, and the target behaviors continued to be controlled.

Case 4.—A 14-year-old boy was brought to the outpatient child psychiatry unit by his foster mother, who complained that the boy had angry temper outbursts from one to five times daily. He would shout, throw objects, and disrupt family life to the point that his foster mother feared he would have to leave. The patient had spina bifida and a meningomyelocele, was able to ambulate with difficulty, and required bladder catheterization. Propranolol therapy (90 mg/day) was begun, along with weekly outpatient psychotherapy.

The primary psychiatrist, foster mother, and patient all thought that propranolol controlled his outbursts of rage, defused the family crisis, and permitted meaningful outpatient psychotherapy. After 6 months, propranolol was withdrawn without recurrence of temper outbursts, although the patient continued to receive counseling for symptoms of adjustment reaction and depressed mood.

Case 5.—A 20-year-old woman with mild mental retardation, a generalized seizure disorder, and intermittent explosive disorder had been expelled from a vocational school because of negativistic behavior, screaming tantrums, and verbal and physical assaults on the staff. She had had viral encephalitis at age 2 years and had sustained a skull fracture at age 3 years. Behavioral problems were long-standing despite consistent discipline and well-qualified care.

The patient required carbamazepine (1,600 mg/day), primidone (1,250 mg/day), and acetazolamide (280 mg/day) for seizure control. Propranolol was added to this regimen, beginning at 20 mg/day and increasing to 240 mg/day during a 7-day period. The aggressive episodes were carefully observed and recorded by the nursing staff. The involved physicians and nurses were convinced that the patient had experienced substantial improvement; thus, she was dismissed while the propranolol dosage was 240 mg/day. Subsequently, she suffered a relapse and was rehospitalized. An adjustment in the propranolol dosage to 300 mg/day resulted in dramatic improvement in her behavior, and she returned to school.

Case 6.—A healthy 30-year-old woman had a bleeding aneurysm of the left middle cerebral artery. During the subsequent few years, multiple complications ensued, including hydrocephaly that necessitated placement of a shunt and then blockage and revision of the shunt. Frontal lobe personality symptoms developed and necessitated institutionalization. The patient acquired "unmanageable" violent outbursts and was assaultive to the staff. She was transferred to our medical center.

Control of assaultive behavior was attempted with haloperidol and then with lithium, without success. Under inpatient supervision, propranolol was added to her antipsychotic regimen, and the dosage was increased to 40 mg orally four times daily. This treatment was accompanied by a decline in pulse rate from 90 to 60 beats/min. The patient was dismissed on a regimen of propranolol, 200 mg/day, and thioridazine, 50 mg daily as needed; her condition was "minimally improved" overall. Her assaultive episodes were thought to be less frequent and less intense than before admission, but she remained uncooperative and difficult.

Case 7.—A 16-year-old boy with mild mental retardation, congenital hemihypertrophy of the left leg, and a seizure disorder underwent evaluation for symptoms of angry outbursts that lasted 3 to 4 hours per day and included verbal and physical aggression. These symptoms had been present since the patient was 2 years old. He had been given trials of methylphenidate, valproic acid, and thioridazine, but the outbursts persisted. Inpatient evaluation coincided with a trial of propranolol (300 mg/day) in addition to valproic acid. Minor provocations continued to elicit shouting, running, and verbal and physical threats. The patient's condition remained unchanged, he was dismissed, and outpatient follow-up was scheduled.

Case 8.—A 48-year-old male accountant had been well until age 30 years, at which time symptoms of bipolar affective disorder had developed. He was treated with a variety of antipsychotic agents and electroconvulsive therapy during the ensuing years, but by age 33, he had clear evidence of neurologic degeneration involving both the cerebrum and the cerebellum.

At age 48, the patient was transferred from a nursing home to an inpatient psychiatric unit because of uncon-

trolled violent outbursts during which he would shout, threaten, throw furniture, and thrash at the staff and other patients. On the ward, he was often mute and incontinent. He was given valproic acid, 250 mg four times daily, for seizure control. Propranolol therapy was begun at 10 mg orally four times daily. The staff noted more frequent and more intense episodes of shouting and thrashing. The propranolol dosage was increased to 80 mg/day and then discontinued after only 10 days of total treatment, because of increasing agitation. He remained agitated after withdrawal of the propranolol regimen and was eventually transferred to another facility.

Comment.—Of these eight patients, two (cases 1 and 2) had complete remission of target behaviors and three (cases 3, 4, and 5) were thought to have substantial improvement. An additional two patients (cases 6 and 7) had minimal or no improvement. One patient (case 8) was thought to have increased agitation while taking propranolol; however, the dosage used was inadequate to achieve β-blockade, as indicated by lack of change in pulse or blood pressure, and the duration of treatment was very brief.

DISCUSSION

The eight cases of intermittent explosive disorder reported herein illustrate several features that are consistent with the reported cases in the literature. The initial response to propranolol may be dramatic, seeming to occur almost overnight (as in cases 1 and 2). This response was specifically noted by Elliott[4] in three of his original cases and has been observed by other investigators as well.[6,36] Greendyke and associates,[9] however, noted a latency period of at least 4 weeks, and Yudofsky and Silver[44] reported that some patients may have a latent period of 6 to 8 weeks before responding to propranolol. Latency of response is difficult to determine with accuracy in all but very dramatic cases because the aggressive behavior in intermittent explosive disorder is, by definition, episodic. Several days may elapse before a change in behavior can be clearly demonstrated to be substantial and lasting. Many authors of reported cases of intermittent explosive disorder have not commented on the number of days or weeks of treatment needed to demonstrate a response. In four of our patients (cases 1, 2, 3, and 5), the response was rapid and sufficiently notable to be apparent during relatively brief hospitalizations of a few weeks. One of our patients (case 4) was seen at weekly intervals and clearly demonstrated a response to propranolol after 2 to 3 weeks of treatment.

Some patients manifest a sensitive threshold response to the dosage of propranolol (as in our case 5), and increases of only 40 to 60 mg/day may be followed by control of symptoms. Elliott[4] also observed this phenomenon.

The association between a therapeutic response to propranolol and β-blockade is unclear. A response to propranolol may coincide with a relative hypotension and bradycardia.[5] Mullane and coworkers[45] reported on the dose of propranolol needed to obtain adequate β-blockade in normal male subjects. They found that plasma levels of 20 ng/ml induced β-blockade in approximately 90% of experimental subjects; this concentration was achieved with dosages of 160 mg/day or less in half of their subjects.

Greendyke and associates[9] reported that "Few positive therapeutic effects from propranolol were noted before doses approaching 300 mg/day were achieved, nor were behavioral improvements identified until treatment had been in progress for at least 1 month." On the basis of these criteria, three of our patients (cases 6, 7, and 8) had inadequate trials to judge the therapeutic efficacy of propranolol. It should also be noted, however, that many patients (perhaps less severely impaired than the population described by Greendyke and associates) require lower doses and less time to respond to propranolol.

Williams and colleagues[8] did not list specific doses used in their series of 30 patients. When we analyzed collectively the 8 Mayo Clinic cases in this report and the 29 cases in the literature for which specific doses were available, we found that the daily doses of propranolol ranged from 60 to 600 mg (mean, 254 mg/day; median, 200 mg/day).* Excluding four nonresponders (our cases 6, 7, and 8 and case 7 reported by Greendyke and associates[9]), we found a mean therapeutic dose of propranolol of 262 mg/day and a median therapeutic dose of 180 mg/day. From these data, it is apparent that a therapeutic response can be achieved at doses much lower than those once reported for treatment of schizophrenia[10] and in the dose range approximating that required for β-blockade.

*These figures and those following do not include the patients in the second study reported by Greendyke and associates.[42]

All the patients in the Mayo Clinic series had some type of central nervous system dysfunction. To date, this is the population that has been reported in the literature as well, with the exception of the case report by Roach and colleagues.[40] A list of reported organic diagnoses in patients with intermittent explosive disorder who have received propranolol is shown in Table 3.

Of the 36 patients for whom specific diagnoses are available, 10 had clinical seizures. In the study of 30 patients reported by Williams and associates,[8] 18 had documented or suspected seizures. Thus, 28 of 67 patients had clinically observed or electroencephalographically demonstrated seizures. Of interest, several authors have described patients who were given propranolol for treatment of dyscontrol symptoms and subsequently had a decline in seizure activity and were able to discontinue taking anticonvulsants.[4,5,8,9] This situation was not assessed in our patients.

On the basis of the variety of diagnoses shown in Table 3, propranolol seems to be exerting some effect on the central nervous system rather than correcting any specific biochemical defect associated with these syndromes. It is unlikely that the improvement noted is due to a sedative effect of propranolol because many of these patients were previously treated with major and minor tranquilizers without resolution of symptoms.

Table 3.—**Organic Diagnoses Recorded for Patients With Intermittent Explosive Disorder Who Have Been Treated With Propranolol***

Diagnosis	No. of patients
Traumatic brain damage	13
Uncontrolled seizures (unspecified cause)	11
Minimal brain dysfunction	9
Other seizure disorder (unspecified cause)	7
Dementia	5
Mental retardation (unspecified cause)	4
Anoxic brain damage	3
Cerebrovascular damage	3
Unspecified "central nervous system dysfunction"	3
Infectious encephalopathy	2
Schizophrenia	2
Huntington's chorea	1
Wilson's disease (hepatolenticular degeneration)	1
Korsakoff's encephalopathy	1
Meningomyelocele	1
No organic diagnosis	1
Total	67

*Includes Mayo Clinic patients.

Propranolol is a highly lipid-soluble agent and readily crosses the blood-brain barrier. It is known to affect the adrenergic, serotoninergic, and dopaminergic systems centrally.[46-48] The report by Mattes[41] of the successful use of metoprolol in two patients with intermittent explosive disorder who did not respond to propranolol is intriguing because metoprolol is a selective β-blocker, lacks membrane-stabilizing effects of propranolol, and is less lipophilic than propranolol.

Propranolol interacts with some antipsychotic agents and increases their circulating plasma concentrations. Peet,[49] who investigated this interaction with chlorpromazine, thought that it accounted for the previously reported successful use of propranolol in the treatment of patients with schizophrenia. Silver and Yudofsky[50] reported a threefold to fivefold increase in thioridazine levels when propranolol was administered concomitantly. Adverse reactions have been reported when propranolol has been used in combination with chlorpromazine[51] and with haloperidol.[52] Of the eight patients we described herein, four received neuroleptics concurrently at some time during their treatment with propranolol. The dose of the neuroleptics was decreased in three patients and discontinued in one. Three of these patients (cases 1, 2, and 3) were among those thought to have substantial improvement. Of the other 28 patients described in the literature for whom this information was provided, 9 received neuroleptics concurrently. This finding indicates that propranolol is an effective agent apart from its synergistic effect with neuroleptics. Nevertheless, the tendency of propranolol to increase blood levels of some antipsychotic agents must be borne in mind when patients are treated—both to forestall serious side effects and to evaluate the therapeutic response accurately.

Silver and Yudofsky[50] described a treatment protocol for the use of propranolol in the dyscontrol syndrome. Among patients who have no condition (such as diabetes or bronchial asthma) that would contraindicate the use of propranolol (Table 4), treatment may begin with 20 mg three times a day. For inpatients, the pulse and blood pressure can be monitored before administration of each dose; if the pulse is 55 beats/min or less or the blood pressure is 90/50 mm Hg or less, the dose should be withheld. The pulse can likewise be monitored in outpatients who require supervision. The propranolol dosage is increased daily or every

Table 4.—**Contraindications to Use of Propranolol**

Raynaud's syndrome
Bronchial asthma
Malignant hypertension
Sinus bradycardia and other arrhythmias
Congestive heart failure
Concurrent use of monoamine oxidase inhibitors
Diabetes mellitus (relative contraindication)

other day until a β-blocking response, such as a substantial decrease in pulse rate or blood pressure, is noted or until a satisfactory clinical response of control of target symptoms is obtained. If no response is observed, a dosage of 640 mg/day maintained for 4 weeks is suggested as an adequate trial. A frequent daily-dosing schedule is used initially to determine the appropriate dose, but when the patient's condition is stable, the regimen may be adjusted to twice-daily dosing. Plasma levels of neuroleptics and anticonvulsants should be monitored, and the doses of these agents should be adjusted as needed. Patients, staff, and family members should be alerted to possible side effects. When propranolol is to be discontinued, the dose should be tapered over 10 to 14 days to avoid rebound hypertension from β-adrenergic release. In some patients with intermittent explosive disorder, the propranolol dose has been tapered after 4 to 6 months of treatment without recurrence of symptoms; other patients require maintenance treatment. There does not seem to be a tolerance effect.

SUMMARY

Several investigators have reported that propranolol is effective for the treatment of intermittent explosive disorder. We describe an additional eight patients with this disorder, five of whom had a complete remission or substantial improvement of their condition with use of propranolol. We await the results of controlled studies of this promising agent.

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