

Neuroreceptor Mechanisms of Aggression and Its Treatment

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Aggression results from the interaction of multiple systems. It can be classified as predatory, impulsive, or based on a medical condition. The likelihood of aggression is increased by environmental overstimulation or stress, transmitter balances favoring dopamine and excitatory amino acid transmission over serotonin and γ -aminobutyric acid transmission, and the presence of problems related to impulsivity. Treatments for aggression are based on the underlying causes and generally should combine pharmacologic and environmental or psychotherapeutic measures. Useful pharmacologic agents include mood stabilizers and atypical antipsychotics that combine dopaminergic and serotonergic actions. Drugs acting on nicotine receptors may deserve further attention. Nonpharmacologic measures include behavioral techniques aimed at reducing impulsivity, relapse prevention techniques for substance abuse, and anger management techniques. (*J Clin Psychiatry* 2003;64[suppl 4]:26–35)

DEFINITIONS OF AGGRESSION AND IMPULSIVE AGGRESSION

Aggression, defined as any behavior that is intended to be destructive to the self, others, or objects, falls into 3 broad categories: premeditated aggression, impulsive aggression, and aggression whose cause is a medical disturbance.¹ Premeditated aggression tends to correspond to animal models of predatory aggression. Impulsive aggression roughly corresponds to irritable or affective aggression in animals; in addition, there are animal models of impulsivity independent of aggression. Treatments for aggressive behavior, especially pharmacologic, tend to focus on impulsive aggression. Premeditated aggression does not lend itself to pharmacologic treatment except in specific circumstances, such as when it is associated with delusional beliefs.²

Impulsivity itself is complex but can be defined as a tendency to act without the ability to consider the consequences to oneself or others.³ Impulsivity is believed to be a failure of a normal process by which, over about one third of a second, a potential behavior is screened before it enters conscious awareness.⁴ The impulsive person is therefore unable to use knowledge or intelligence to shape behavior.

Impulsive aggression therefore has certain basic characteristics, which will help us to understand its identification, mechanisms, and treatment: (1) the response is rapid, (2) there is no opportunity for reflection about the behavior, and (3) the behavior is not appropriate to its context. It is typically carried out without likelihood of benefit and may be followed by bewilderment or remorse.

Two factors add complexity to this picture. First, the same individual may carry out both impulsive and planned aggressive acts. Second, over time, individuals may adapt to the impulsive pattern over which they have little control. They may develop a lifestyle that incorporates impulsive aggression and other impulsive acts, for example, or may learn, after a premeditated act, to feign the bewilderment that follows impulsive aggression.

Impulsivity lies in a pattern of behavior; no act is impulsive in and of itself. For example, an impulsive person may do many things that reflect poor judgment or are risky. However, impulsivity is not poor judgment, which implies reflection and decision making that is faulty. *Impulsivity* means acting without reflecting or deciding. Similarly, impulsive behavior does not seek risk but ignores it.

TRANSMITTER MECHANISMS OF IMPULSIVE AGGRESSION

I review some transmitter systems that are involved in aggression and impulsivity and that may be relevant to treatment. This review is not intended to be exhaustive.

Serotonin

There is much evidence relating low serotonin function to increased impulsivity and aggression,^{5,6} but its role is

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complex, with different effects across receptor subtypes⁷⁻⁹ and even between hemispheres.¹⁰ Increased impulsivity resulting from lesions that deplete serotonin,^{8,9} or ablation of the serotonin-1B receptor gene,¹¹ apparently stems at least partially from release of dopaminergic activity from serotonergic inhibition. Clinical studies have shown impulsivity to be associated with low serotonergic function in humans.^{12,13} In aggression and in suicide attempts, the serotonergic deficit appears to be associated more closely with impulsivity than with aggression or suicidality per se.¹⁴ Most studies¹²⁻¹⁵ linking serotonin to impulsivity were carried out in subjects with chronic conditions like personality disorder, in healthy controls, or in those with major depressive disorder. As noted by Asberg,¹⁵ the relationship between serotonin and impulsivity appears weaker in bipolar disorder.

The low serotonergic function associated with increased risk or incidence of impulsive behaviors, including suicide and impulsive aggression,^{12,13} is not specific to time; that is, detection of a serotonergic deficit does not seem to tell us exactly when someone will commit a severely impulsive act. Generally, deficits in serotonergic function were measured at times that were remote from the index impulsive behavior.¹⁶⁻¹⁸ Effects of tryptophan depletion and loading, which decreases or increases serotonin function, respectively, also correlate with stable personality traits, with a larger effect in previously aggressive individuals.¹⁹ Low serotonin may predispose to impulsivity as a stable characteristic, but some other more variable factor may be associated with immediate risk for impulsive behavior.

Catecholamines

Catecholamines are generally associated with increased impulsivity. The most consistent increases in impulsive behavior in animal models are caused by stimulants.²⁰⁻²⁴ Stimulants also increase impulsivity in humans who do not have an attention disorder.²⁵ Risk of impulsivity is associated with abnormal regulation of catecholamine metabolism, reflected by low monoamine oxidase.²⁶⁻²⁹ Increased risk of impulsive behavior may be associated with elevated dopaminergic^{30,31} or noradrenergic function.³²⁻³⁵

Dopamine may mediate stimulant effects on impulsivity in animal models¹¹ and has a prominent role in motivation and the initiation of behavior. It increases aggression in most animal models. A central nervous system (CNS) metabolite, homovanillic acid (HVA), is increased in cerebrospinal fluid (CSF) in manic episodes although it does not correlate with symptoms of mania.³⁶ Results of studies using serotonin depletion in rats^{8,9} or receptor knockout mice¹¹ suggest that trait impulsivity may result from a balance between dopamine and serotonin, in which animals with serotonin depletion or receptor deletions are impulsive due to release of a dopaminergic activation system from serotonergic inhibition.

Changes in noradrenergic activity may induce rapid fluctuations in impulsivity associated with overstimulation or stress. Noradrenergic pathways from the locus ceruleus project diffusely to cerebral cortex, cerebellum, limbic system, and spinal cord; this system is sensitive to sensory stimulation, stress, and novelty.³⁷ Effects of norepinephrine on the prefrontal cortex depend on the noradrenergic alpha-1/alpha-2 stimulation ratio. With stress or other conditions of noradrenergic excess, excessive alpha-1 stimulation may take the frontal cortex "off-line,"³⁸ potentially inactivating a behavioral screening system.⁴ Therefore, rapid changes in impulsivity could result from fluctuations in noradrenergic function superimposed on a balance between dopaminergic and serotonergic function.³⁹

Excitatory and Inhibitory Amino Acids: Relationship to Arousal

Impulsivity results from a failure to balance the generation and the screening of action. This can occur for 2 basic reasons: (1) the screening mechanism might fail, and (2) the generation of behavior may be excessive or poorly regulated. The balance between generation and screening of behavior may be related to a balance between dopamine, with a strong role in activation and the initiation of behavior, and the inhibitory role of serotonin.⁴⁰

The efficient screening of behavior requires efficient scanning of the environment, both internal and external. This requires that the regulation of attention and arousal be intact. Arousal is a complex phenomenon that involves multiple interactions among catecholamines, serotonin, acetylcholine, and amino acid transmission.⁴¹ Two transmitter systems play key potential roles in this aspect of impulsivity. First, as noted above, noradrenergic stimulation may be associated with susceptibility to impulsivity in times of stress or of overstimulation. Second, the level of arousal depends on the balance between excitatory (glutamate) and inhibitory (γ -aminobutyric acid [GABA]) amino acid function.⁴² An imbalance in the direction of excitatory amino acid function would predispose to overstimulation; an imbalance toward inhibitory amino acid function would predispose to impaired attention and disinhibition. Consistent with this, stimulation of glutamate receptors appears to facilitate aggressive behavior.⁴³ While GABA effects are complex, depending on the state of the animal, previous treatments, and the model of aggression,⁴⁴ GABA agonists appear in general to reduce both predatory⁴⁵ and affective^{46,47} aggressive behavior in animals.

Human studies also suggest a relationship between impulsive aggression and the regulation of arousal.⁵⁰ One example of this is the relationship between impulsivity and anxiety. Barratt has shown that impulsivity and anxiety are orthogonal, that is, basically independent of each other.^{49,50} However, increased arousal, stress, or overstimulation can produce both anxiety and impulsivity. Anxiety, at least in depression, is associated with increased hostility in men.⁵¹

Impulsivity and impulsive aggression can also be associated with panic-like states.⁵² Anxiety and impulsive aggression may be basically independent behaviors, but they can be driven by similar mechanisms.

In addition to direct effects on processes related to impulsive aggression, regulatory interactions between systems are potentially important. For example, increased GABA function would tend to reduce a tendency toward overstimulation. In addition, GABA interneurons inhibit firing of mesolimbic and mesocortical dopaminergic cells.^{53,54} Enhancement of GABA function, therefore, might interact synergistically with reduction of dopaminergic activity in reducing impulsive aggression.

Acetylcholine

Nicotinic. Among its many behavioral and cognitive effects,⁵⁵ nicotine reduces both predatory and affective aggressive behavior in animals.⁵⁶⁻⁵⁸ These effects may involve indirect interactions with serotonergic systems.⁵⁹ Nicotine reduces behavioral laboratory aggression in humans.^{60,61} Tobacco withdrawal is associated with increased aggression and irritability in humans^{62,63}; the severity depends on the strength of the urge to smoke and on the individual's preexisting aggressiveness.⁶³ Nicotine gum reduces the aggressiveness associated with tobacco withdrawal, while placebo gum has no effect.⁶²

Muscarinic. While results vary based on the model of aggression, stimulation of muscarinic receptors, or increased cholinergic function in general, is generally associated with increased predatory and affective aggression in animals.⁶⁴⁻⁶⁶

Gonadal Steroids

Increased levels of testosterone appear to be associated with aggression and less consistently with impulsivity in a variety of human and animal studies. Their roles in pathologic aggression may differ from those in normal behavior. Elevated concentrations of testosterone have been reported in delinquents,⁶⁷ violent alcoholics,⁶⁸ aggressive normal subjects,⁶⁹ and aggressive nonhuman primates.⁷⁰ Interestingly, plasma testosterone levels correlated with impulsiveness in women.⁷¹ Exogenous testosterone increased aggressive responses on behavioral laboratory tests in normal humans,^{72,73} but effects were highly variable.⁷³

Implications for Treatment

Based on information already presented, there could be no single optimal treatment for all aggression. Questions that influence treatment are shown in Table 1. Based on these factors, optimal treatment must generally combine environmental and pharmacologic strategies, addressing immediate and longer-term needs. Before general treatment strategies are discussed, characteristics of aggression and impulsivity in specific psychiatric problems in which they are prominent are reviewed.

Table 1. Factors That Influence Treatment Decisions in Aggression and Impulsivity

Premeditated or impulsive?
Caused by a nonpsychiatric medical condition (toxicity, withdrawal, delirium, dementia, infection, metabolic abnormality)?
Associated with a DSM-IV Axis I psychiatric disorder?
Associated with a personality disturbance?
Acute/fluctuating or chronic?
Prominent overstimulation?
Environmental context: legal, relationship, and/or economic problems?
Personal context: personality characteristics, conflicts?

IMPULSIVITY AND IMPULSIVE AGGRESSION IN MAJOR PSYCHIATRIC DISORDERS

Impulsivity and aggression are not limited to any specific disorder or even to the presence of a "disorder." A brief review of the major diagnostic groups in which aggression and impulsivity are prominent, except for disorders of childhood and adolescence and dementia disorders, which are specifically discussed elsewhere in this supplement, follows.

Personality Disorders

Personality disorders may predispose to either impulsive or premeditated aggression. Impulsivity is prominent in the cluster B personality disorders: borderline,⁷⁴ antisocial,^{75,76} narcissistic, and histrionic. The last 2 disorders are less studied than the others. In addition to impulsive aggression, individuals with personality disorders may carry out premeditated aggression related to their interpersonal distortions.

Substance Use Disorders

Most commonly abused substances have been reported to elicit increased impulsivity or aggression, especially alcohol and stimulants.^{25,77} Withdrawal from sedatives or alcohol can also elicit agitation with increased risk for aggression and impulsivity. The likelihood that a drug will elicit aggression is dependent in part on the individual; for example, alcohol is more likely to elicit aggression in those who have previously been aggressive.⁷⁸

Impulsivity also appears to predispose to substance use disorders. A study of cocaine users found that aggression in these subjects was related to their characteristics before cocaine use, rather than to characteristics of their cocaine abuse itself.⁷⁹ Cocaine users were found to be more impulsive than comparison subjects⁸⁰ regardless of the presence of cluster B personality disorders or histories of aggressive behavior.

Schizophrenia

Patients with schizophrenia can be more susceptible to impulsive aggression during overstimulation, agitation, and psychosis.⁸¹ Aggression in schizophrenia is associated with greater severity of illness overall.^{82,83} Patients with

schizophrenia may carry out premeditated impulsive acts due to delusions or psychotic misinterpretations of their surroundings.² Conventional antipsychotic treatments can also potentially increase the risk for agitation or aggression by causing akathisia, which can be associated with severe exacerbations of symptoms⁸⁴ or even suicide attempts.⁸⁵ The risk of this complication is reduced, although not eliminated, by the use of atypical antipsychotics.

Nicotine withdrawal may also exacerbate behavior problems in schizophrenia, particularly with the trend toward smoke-free medical facilities. Tobacco use is higher in schizophrenia than in controls or in any other psychiatric disorder.^{86,87} This increase in smoking may have a component of self-treatment, since nicotine appears to decrease gating deficits and other cognitive and sensory abnormalities in schizophrenia.^{88,89} Concomitant use of a nicotine patch improved cognitive function in patients treated with haloperidol.⁹⁰ As noted above, tobacco withdrawal can exacerbate aggressive behavior in newly hospitalized patients with schizophrenia.⁶³

Bipolar Disorder

Impulsivity is prominent in bipolar disorder. It is nearly impossible to meet diagnostic criteria for a manic episode, the hallmark of bipolar disorder, without overtly impulsive behavior.⁹¹ There is also a prominent distinction between state and trait impulsivity in patients with bipolar disorder. Euthymic patients, compared with controls, have elevated Barratt Impulsiveness Scale scores, but score normally on behavioral laboratory measures of impulsivity.⁹² During manic episodes, behavioral laboratory impulsivity is also increased.⁹³ Increased risk of aggression in mania may be associated with the increased noradrenergic and dopaminergic transmission that characterizes manic episodes.³⁵

Smoking is increased in bipolar patients compared with the general population,^{89,94} and tobacco withdrawal can potentially worsen aggressive behavior in manic patients. In addition, nicotine withdrawal mania has been reported.⁹⁵

In addition to impulsive aggression, patients with bipolar disorder may carry out premeditated aggressive acts due to delusions or distortions associated with depressive, manic, or mixed episodes.²

Impulsivity and Multiple Diagnoses

Impulsivity may be responsible for combinations among the above diagnoses. The incidence of substance use disorders is increased in patients with bipolar disorder, schizophrenia, or personality disorders. There is also prominent overlap between bipolar disorder and cluster B personality disorders.⁹⁶ Risk of aggression, impulsivity, and suicide is higher in patients who have combined disorders.^{97,98} These conditions may share common physiology related to susceptibility to impulsivity.³

Table 2. General Principles in the Management of Aggression

1. Assure the safety of the patient and staff
2. Determine whether any medical condition is present that could be causing the behavior, contributing to it, or obscured by it. This is vital even if there is a known DSM-IV Axis I or II diagnosis
3. Be alert to possibilities of drug intoxication, withdrawal (including nicotine withdrawal), toxicity, or pharmacokinetic interactions, including those between prescribed and nonprescribed drugs
4. Obtain information from all possible sources
5. Maintain an appropriate level of environmental stimulation

MANAGEMENT OF AGGRESSION

Specific treatments and emergency management are discussed in detail elsewhere in this supplement. The focus here is on principles based on the mechanisms of aggression discussed above and their application to treating aggression in schizophrenia.

General Principles

Basic principles of the management of aggression are shown in Table 2. In addition, treatment may vary over the time course of a problem: (1) acute treatment of a medical or situational problem, (2) treatment of an exacerbation of a chronic/recurrent illness, and (3) long-term management of a chronic problem. Each of these requires a complementary balance between pharmacologic and nonpharmacologic treatments.

Pharmacologic Treatments for Impulsive Aggression

Based on mechanisms discussed so far, treatments for impulsive aggression could have the following basic mechanisms: (1) enhancing an inhibitory system, such as serotonin; (2) inhibiting an activating system, such as dopamine; (3) stabilizing fluctuations in inhibitory and/or excitatory systems; and (4) protecting against overstimulation or normalizing arousal. Many, perhaps most, treatments work by more than one of these basic mechanisms. Combinations of treatments working on different mechanisms may have synergistic effects.

Lithium. Lithium may be the first treatment reported to have a specific, non-sedative effect on impulsive aggression. Lithium has been reported to reduce impulsive aggressive behavior across a range of diagnoses and situations,⁹⁹ from prisoners¹⁰⁰ to subjects with conduct disorders.¹⁰¹ Lithium works in part by enhancing serotonergic activity¹⁰² but probably combines other mechanisms. It has been shown to be effective in treating impulsive aggression across a broader range of contexts than any other agent, although it may worsen interictal aggression in subjects with temporal lobe epilepsy.¹⁰³ Lithium's onset of action is gradual, so it is suitable for subacute or chronic, but not acute, treatment.

Serotonin enhancers. The most commonly used serotonin enhancers are selective serotonin reuptake inhibi-

tors, although 5-HT_{1A} agonists and 5-HT₂ antagonists also fit in this category, as has the serotonin precursor tryptophan in places where it is available. These medicines have been reported to be effective in treating chronic forms of impulsive aggression in cluster B personality disorders and as an adjunct to antipsychotic treatments in schizophrenia.¹⁰⁴ They appear less suitable in disorders related to bipolar disorder, psychosis, or other situations where overstimulation is prominent. Like lithium, they have gradual onset of action and are suitable for subacute or chronic, not acute, management.

Anticonvulsants. Anticonvulsants may work by altering the GABA-excitatory amino acid balance in favor of GABA by protecting against overstimulation, and, where aggression is associated with a seizure disorder, raising the convulsive threshold. Most evidence supports phenytoin, carbamazepine, and valproate.

1. Phenytoin. Phenytoin was reported to be more effective than placebo in impulsively aggressive inmates.¹ It was not effective in premeditated aggression. Subjects who improved also had increased amplitude of the auditory P300 potential.¹

2. Carbamazepine. Carbamazepine has been reported to be effective in subjects with head injuries^{105,106} but did not differ from placebo in a group of subjects with conduct disorder; side effects were common.¹⁰⁷ Carbamazepine has been used as an adjunct in aggression associated with psychosis or severe agitation, but a critical review of these studies concluded that the evidence did not support its use.¹⁰⁸

3. Valproate. Valproate has been reported to be effective against impulsive aggression and/or hostility in borderline subjects with bipolar II disorder,¹⁰⁹ borderline subjects in 2 placebo controlled studies,^{110,111} and adolescents with aggression and labile mood in 1 open¹¹² and 1 controlled¹¹³ study. A review of earlier evidence in nonbipolar subjects found it to be effective in 77% of 164 subjects in 17 studies, but these were open studies that often included more than 1 treatment.¹¹⁴ Agents that increase serotonergic function may have a complementary role with mood-stabilizing drugs since divalproex was reported to decrease aggressive behavior in subjects with impulsive aggression and personality disorders who had not responded to fluoxetine.¹¹⁵

Anticonvulsants are generally suitable for subacute or chronic treatment, although rapid stabilization with intravenous divalproex has been reported in severe agitation¹¹⁶ and in catatonia.¹¹⁷

Antipsychotic drugs. Antipsychotic drugs are among the most effective means for pharmacologically reducing overstimulation and are considered to be effective in treating aggression in a wide range of conditions, usually associated with psychosis or mania. Usefulness of conventional antipsychotic agents is limited by extrapyramidal effects and akathisia. There is also risk of hyperthermia or neuroleptic malignant syndrome in patients who are restrained

and struggling in poorly ventilated seclusion rooms. Treatment should be aimed at specific target symptoms rather than "chemical restraint."¹¹⁸

There has been much interest in atypical antipsychotics, including clozapine, risperidone, olanzapine, quetiapine, and ziprasidone, due to their reduced incidence of movement disorders (especially akathisia) and their serotonergic effects. Perhaps the most-studied agent is risperidone.^{119,120} The most extensive evidence, but a lack of controlled trials, supports clozapine,^{121,122} which seems to have specific anti-aggressive effects in animals¹²³ and clinical anti-aggressive effects that are independent of its antipsychotic effects.¹²⁴ Clozapine is not generally feasible as a first treatment, however. Initial antipsychotic treatment is generally likely to be with one of the more widely used atypical antipsychotics or a conventional neuroleptic, perhaps as part of a combination of treatments as described below.

Antipsychotic agents can be useful for rapid treatment of aggression, impulsivity, and hostility associated with psychotic episodes, mania, or overstimulation. They are useful for prolonged treatment if they are needed to treat an underlying chronic psychiatric disorder.

Anti-noradrenergic agents. Use of β -blockers in conjunction with antipsychotic treatments is discussed below. β -Blockers have been reported to be effective in reducing aggressive behavior in dementia, attention deficit disorders, personality disorders, posttraumatic stress disorder, and closed head injury in addition to schizophrenia.¹²⁵

Stimulants. Effects of stimulants on aggression demonstrate the manner in which pharmacologic responses depend on the rate-limiting step of a behavior. In people with attention-deficit/hyperactivity disorder or other developmental problems where impairment of attention apparently increases susceptibility to impulsive behavior, stimulants reduce impulsivity or aggression.¹²⁶⁻¹²⁸ In individuals without such problems, stimulants increase impulsivity^{25,77} and, possibly, aggression.¹²⁹

Sedatives. Benzodiazepines, the safest sedatives, may reduce agitation and behavioral problems associated with severe overarousal or anxiety.¹¹⁸ Onset of action of the more lipid-soluble benzodiazepines is relatively quick, and they are generally well tolerated. However, disinhibition can occur with benzodiazepines, especially in patients who are old or who have an organic disorder.¹³⁰ Benzodiazepines may act synergistically in combination with antipsychotic agents, making it possible to use lower doses than would be required with either agent alone.¹³¹ Intravenous diazepam was reported to rapidly reduce severe akathisia.¹³²

Benzodiazepines are potentially useful for acute treatment. Value of subacute or chronic treatment is limited by cognitive effects, tolerance, and potential for abuse.

Endocrine treatments. Anti-androgen treatments, including medroxyprogesterone and leuprolide, have been

used successfully in aggression associated with dementia¹³³⁻¹³⁵ and posttraumatic brain injury.¹³⁶ Evidence for these treatments is mostly from open-label studies, but there have been 3 successful blinded studies.¹³⁷ In addition to pathologic aggression, estrogens may have a range of behavioral effects in affective disorders and in Alzheimer's disease, but there is little evidence from convincingly designed studies.¹³⁸

Combined treatments for aggression in psychotic disorders. Combinations of agents with different mechanisms may be more effective than treatments with single agents, especially in more complex situations such as aggression associated with psychotic disorders. The major classes of treatments used in conjunction with antipsychotic treatments have been lithium, anticonvulsants, serotonin-enhancing drugs, and β -noradrenergic antagonists. Some of these combinations are based on interactions between dopamine and GABA^{53,139} or dopamine and serotonin.¹⁴⁰

Antipsychotic treatments have been combined with "mood-stabilizing" drugs. Lithium was shown to provide a modest benefit after 5 weeks of combined treatment with antipsychotic drugs, but occasionally produced "somnambulistic-like" episodes and other adverse neurologic effects.^{141,142} Several reports of carbamazepine reveal modest effects at best, possibly hindered by induction of oxidative metabolism of the antipsychotic drug.^{108,143} There are open-label reports of possibly favorable effects of lamotrigine¹⁴⁴ and topiramate.¹⁴⁵ Results with valproate have been the best documented, including augmentation of response to haloperidol and to atypical antipsychotics in placebo-controlled trials.¹⁴⁷⁻¹⁴⁹ These results are consistent with synergistic effects of dopamine blockade and GABA enhancement.^{53,139}

Serotonin reuptake blockers have been used in attempts to reduce aggressive behavior and depression-like negative symptoms. Fluvoxamine was reported to reduce negative symptoms and aggression in some patients, although the authors felt that better definition of patients likely to benefit was needed.¹⁵⁰ Citalopram reduced aggressive incidents in a placebo-controlled crossover study.¹⁰⁴ Doses needed for augmentation of antipsychotic treatments were considered to be lower than those for conventional antidepressive effects.

β -Blocking agents have been used both to reduce neurologic side effects of antipsychotic drugs and to reduce aggressive behavior. Nadolol reduced extrapyramidal effects and aggressive behavior relative to placebo.¹⁵¹ Pindolol reduced aggression as measured by the Overt Aggression Scale but did not alter symptoms of psychosis.¹⁵²

Nonpharmacologic Management of Aggression

Pharmacologic and nonpharmacologic strategies have synergistic roles in the management of aggressive behavior. Acute and chronic treatment have overlapping but different needs.¹⁵³

Acute nonpharmacologic strategies.

1. Interpersonal. It is vital for all staff members to be consistent in their communications and that appropriate interpersonal boundaries are maintained. Outcome is influenced by interpersonal styles of nursing staff, with empathic styles of intervention having better outcomes.¹⁵⁴

2. Environmental. The patient should have privacy and maintenance of an appropriate level of environmental stimulation. In general, this means protection against overstimulation. Acutely agitated patients were found to have better treatment outcomes in settings where individual attention was maximized and group interactions were reduced.¹⁵⁵

Chronic nonpharmacologic strategies.

1. Educational. When relevant, patients must learn the roles of overstimulation or other environmental factors in behavioral problems and must learn to recognize early warning signs and use medicine and other strategies to defuse problematic situations early.

2. Behavioral and cognitive-behavioral therapies. Anger management,¹⁵⁶ dialectic behavioral therapy (in borderline or related disorders),¹⁵⁷ and relapse prevention therapies^{158,159} can work synergistically with pharmacologic treatment to improve participation in treatment and outcome.

CONCLUSIONS

Effective treatment of aggression depends on ascertaining the cause or causes and aiming treatments rationally at the rate-limiting steps of the behavior. Pharmacologic treatments reduce aggression or impulsivity, and normalize arousal, by shifting the balance of amino acid neurotransmission away from excitatory transmission and toward inhibitory (GABA), reducing dopaminergic activity, enhancing serotonergic function, and/or reducing or stabilizing noradrenergic effects. Combinations of these approaches, such as combined GABA enhancement and dopaminergic blockade, may be optimal. Definitive treatment must also be aimed at illnesses, psychiatric or otherwise, that may cause or abet the aggressive behavior.

Optimal treatment also requires an appropriate environment, with protection against overstimulation and harm, consistent communications, and effective but empathic limit-setting.

Long-term treatment requires the effective pharmacologic and nonpharmacologic treatment of underlying chronic or recurrent illnesses, combined when needed with behavioral strategies aimed at reducing aggressive or impulsive behavior.

Drug names: carbamazepine (Tegretol, Eptol, and others), citalopram (Celexa), clozapine (Clozaril and others), diazepam (Valium, Diastat, and others), divalproex sodium (Depakote and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), haloperidol (Haldol and others), lamotrigine (Lamictal), leuprolide (Viadur, Lupron, and

others), medroxyprogesterone (Prempro, Provera, and others), nadolol (Corgard, Corzid, and others), olanzapine (Zyprexa), phenytoin (Dilantin), pindolol (Visken and others), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), ziprasidone (Geodon).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, carbamazepine, citalopram, clozapine, diazepam, fluoxetine, haloperidol, lamotrigine, leuprolide, medroxyprogesterone, nadolol, olanzapine, phenytoin, pindolol, quetiapine, risperidone, topiramate, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of impulsive aggression, aggression, and impulsivity.

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