

The Role of Typical and Atypical Antipsychotic Medications in the Management of Agitation and Aggression

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The management of agitation and aggression in psychiatric inpatients is a significant clinical dilemma. Establishing a clear diagnosis and distinguishing whether aggression is an acute manifestation or a long-standing or repetitive problem are fundamental antecedents of medication treatment. For acute aggression, either benzodiazepines or antipsychotic medications (typical and atypical) are recommended choices. Currently, on the basis of efficacy, ease of use, and availability in multiple (tablet, liquid, intramuscular) preparations, typical antipsychotics such as loxapine should be considered as first choice for acute aggression (in psychosis). On the other hand, atypical antipsychotics, particularly clozapine, should be considered when aggression in psychosis persists and/or is repetitive. Typical antipsychotics are indicated for persistent aggression in psychosis when medication noncompliance is the obstacle to effective treatment.

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Few issues provoke such public outcry as the occurrence of violence in a person with mental illness. Incidents receive high profile, often with a biased and inaccurate portrayal of mental illness.¹ It is hardly surprising that public opinion continues to reflect the notion of a fundamental link between aggression and mental illness. Aggression is the single most detrimental factor in the continued stigmatization of mental illness. Rather than serving as a catalyst for change and more progressive treatment, public responses often assert the need for more social control and longer periods of institutionalization for persons with serious mental illness. Amid such responses, many professionals feel bewildered and stigmatized by the public scrutiny that ensues when violent episodes occur. On the other hand, there is concern that some mental health clinicians may minimize this relationship and in doing so underestimate the predictability of violence in persons with serious mental illness.

In addition to the broader political and social context of violence and mental illness, the economic impact of aggression in patients is substantial. In one state hospital study, lost days from disability among 24 staff members

cost \$766,290 over a 1-year period.² In another study, inpatient violence cost \$38,000 during 1 year.³ There are also costs associated with the high-intensity management (e.g., 1-to-1 nursing, medical consultations, x-rays) of these aggressive patients. Although hospital administrators and nursing staff are cognizant of these sequelae, the economic and staffing impact of aggression is not generally appreciated by clinicians.

WHICH PATIENTS ARE AT RISK FOR VIOLENT BEHAVIOR?

There are now substantial and credible data from epidemiologic studies that highlight a higher rate of aggression in persons with mental illness.⁴⁻⁸ These data are reinforced by studies of jail populations⁹ and of persons who commit homicide¹⁰; on the aggregate, these confirm the association between violence and mental illness. However, far more notable is the (alternative and entirely complementary) perspective that the majority of individuals with mental illness are not violent; moreover, the contribution of mental illness to violence at large is small.¹ Thus, violence in mental illness is not a "class effect." Rather, it is confined to distinct patient and diagnostic groups and, within each of these groups, to only a small proportion of patients. These distinctions are highlighted in Table 1.

Four clinical characteristics contribute overwhelmingly to the risk of violence among persons with serious mental illness: (1) acute, poorly controlled illness; (2) noncompliance with medication; (3) substance abuse; and (4) past history of violent behavior. Each of these is an independent risk factor for aggression in psychosis. However,

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Table 1. Aggression in Patients With Mental Illness

Disorder	Violence	
	Episodic/ Persistent	Concomitants ^a
Schizophrenia	Either	Most often related to active psychosis; substance abuse and noncompliance as major risk factors
Bipolar	Usually episodic	Most often during manic episode; violence during depression usually related to psychotic features; substance abuse and noncompliance as major risk factors
Delusional	Episodic	Focused on delusional subject, eg, erotomantic delusions; a direct challenge to delusional system may precipitate extreme episodic violence, eg, unrequited love in a patient with erotomantic delusion
Dementia	Either	Unfocused; related to fluctuations in mental status
Personality and impulse control Intermittent explosive Borderline Antisocial	Either	Substance abuse as complication; related to chaotic interpersonal relationships and life crises
Organic states Head injury Infective Metabolic/ drug toxicity	Either	Related to fluctuations in mental status; frontal and temporal lobe brain damage associated with more violent and persistent aggressive behavior

^aFactors associated with violence in the general population (e.g., age, gender, history of childhood abuse, aggression as a child, truancy) are also pertinent to the relationship between mental illness and violence.

more often than not, these features co-occur and synergize to heighten the risk for both the occurrence and repetition of violent behavior.

Most patients with schizophrenia who commit violent acts are psychotic at the time of the incident.^{11,12} In one recent evaluation of patients in a maximum security forensic hospital, over 75% of those with a psychosis were noted to have been compelled by their delusion to offend.¹⁰ It is also recorded in several studies that the risk of violence is at a maximum during acute relapse.^{8,12-14} This risk is present both before and immediately after hospitalization.^{13,14}

Noncompliance with medication is a frequent problem among persons with serious mental illness, with recent estimates suggesting that approximately 80% of patients are noncompliant at some time during their illness.¹⁵ However, it is important to appreciate that even though noncompliance is common, it is nevertheless (of itself) a risk factor for violence.⁷ Recent efforts to minimize noncompliance include the use of cognitive-behavioral approaches,¹⁶ so-called "compliance therapy," the use of psychiatric advance directives, and (even more contentious) outpatient commitment.¹⁷

Substance abuse, often inextricably linked with poor medication compliance, is also a major risk factor for violence.^{7,18-20} This association is well illustrated in the Epi-

Table 2. Violence Risk Assessment for Patients With Schizophrenia

History of abuse as a child
Past history of violence toward others
Substance abuse history
Noncompliance with medications
Current behavior
Level of agitation
Possession of weapons
Evidence of threatening behavior
Current mental status
Perceived threat
Persecutory delusions, identifying specific individual
Delusions of control
Statement of intent to harm
Command hallucinations
Disorientation

demologic Catchment Area (ECA) study.⁴ Persons with psychosis were shown to be 5 times more likely than the general population to commit violent acts, persons with substance abuse disorder were 10 times more likely, and persons with dual diagnosis were 17 times more likely. Another recent study reported that schizophrenic patients with comorbid substance abuse were 8 times more likely to be violent than schizophrenic patients who did not abuse drugs or alcohol.²⁰ Substance abuse may increase the risk of violence through heightened exposure to threatening circumstances (e.g., drug dealing), through worsening of psychotic symptoms (either directly or via concomitant neuroleptic noncompliance), through the superimposition of acute intoxication and drug withdrawal effects (e.g., phencyclidine hydrochloride [PCP] intoxication), through cognitive impairment and diminished frontal executive control, and, more speculatively, perhaps through some modulation of the serotonergic system.

Finally, it is well recognized that a past history of aggressive behavior is the best predictor of future violence.^{11,21-23} This is why so much emphasis is placed on clinicians being well-trained in violence risk assessment.²² Assessment elements for risk of violence in persons with schizophrenia are highlighted in Table 2.

What can we conclude from all of the above? A proportion of persons with serious mental illness are aggressive, and these patients are characterized by a higher risk of untreated illness and by active substance abuse. Thus, violence among persons with mental illness should be viewed in a clinical (and not merely an epidemiologic) context that emphasizes the need for rapid and effective control of symptoms of illness. Taylor has succinctly captured this sentiment: "Among people with schizophrenia in particular, the risk of violence is almost invariably due to the illness and thus can generally be managed. Often it is not managed, and the person with schizophrenia has to bear the brunt of that burden as well as the symptoms of the illness."^{12(p166)}

PHARMACOLOGIC MANAGEMENT OF AGGRESSION

At the present time, there is no agent approved and licensed for the management of aggressive behavior. A variety of psychotropics from different classes have been tried.^{24,25} The rationale for the use of each agent reflects the (limited) current understanding of the neurobiology of violence and the likely involvement of multiple neurotransmitter systems in serotonin, dopamine, GABA, and norepinephrine.²⁴ It should also be pointed out that pharmacologic studies on aggressive patients are extremely difficult to conduct. Serious obstacles include ethical concerns, the validity of informed consent, and the lack of appropriate research settings (i.e., most aggressive patients receive long-term care in state facilities that are generally ill-equipped to conduct such research).²⁴ Accordingly, much of the reported literature is based on augmentation trials, most often as case series rather than more rigorous clinical trials. Given the importance of the issue of violence in the acute management of mental illness, it is surprising (notwithstanding the aforementioned obstacles) that this area has received such little attention and has not been a target for clinical trials. Described below are pharmacologic options for treating aggression in psychosis. Some reference is made to the role of these drugs for aggression in other conditions, although such approaches are not well studied. Accordingly, the predominant focus here is on aggression in psychosis.

Typical Antipsychotics

Typical antipsychotics, particularly high-potency agents, have been the mainstay of the treatment of aggression, especially in the context of active psychosis.²⁵ Until a few years ago, haloperidol was the most commonly prescribed antipsychotic medication and was used for psychosis and also more broadly for the management of agitation in a variety of settings—acute medical care facilities, nursing homes, head trauma centers, and mental retardation treatment facilities. Haloperidol and related antipsychotics have sedative and antipsychotic effects. It is unclear whether they selectively target aggression independent of these properties. High- and mid-potency antipsychotics have been preferred, since low-potency antipsychotics are more likely to cause sedation, confusion, anticholinergic toxicity, and postural hypotension. In some instances, mid-potency agents are preferred because they are more sedative than haloperidol. There have been few head-to-head studies comparing efficacy in treating aggression between typical antipsychotics (see below). However, typical antipsychotics are often prescribed in inordinately high doses to patients with schizophrenia who are violent, despite the absence of efficacy in controlling aggression in such patients.²⁶ Moreover, high-dose neuroleptic therapy has been shown to aggravate aggression²⁴—probably by worsening

akathisia. Thus, high-dose neuroleptic therapy is no longer viewed as acceptable pharmacologic management.²⁷

Atypical Antipsychotics

There is evidence that novel antipsychotics may be of benefit in managing aggression.²⁸ Thus far, most of the work has been confined to patients with schizophrenia, although there are isolated reports of the benefit of these drugs for agitation in nonpsychotic conditions²⁹ and in behavioral disturbance in dementia.³⁰

Clozapine. When clozapine became available in state facilities in the United States, clinicians noted a decline in rates of seclusion and restraint and in the use of emergency (p.r.n.) medications. Additionally, patients who had been hospitalized for years because of persistent aggression were under better behavioral management and were able to be discharged. The low rates of rehospitalization of such patients to state facilities are well documented and of substantial economic impact.³¹ Wilson³² documented dramatic and sustained reductions in seclusion and restraint in 37 long-stay patients with schizophrenia. Ebrahim and colleagues³³ reported the total cessation of seclusion and restraint during the first 6 months of clozapine therapy in 27 patients. Chiles and colleagues³⁴ noted that this effect on seclusion and restraint began between weeks 2 and 4 of therapy and was sustained for the year in 115 patients receiving a mean dose of 700 mg of clozapine. Similarly, Mallya and colleagues³⁵ noted a 90% reduction in seclusion over a 13-month period in 107 schizophrenic patients. Several other studies have noted this effect.³⁶⁻⁴⁰ The literature is thoroughly reviewed in a recent article by Glazer and Dickson.⁴¹

The consistency of this observation across several studies raises the question as to whether clozapine possesses a specific antiaggressive effect. In a study of this issue, Volavka and colleagues³⁷ examined the hostility and psychosis scores derived from serial Brief Psychiatric Rating Scale (BPRS) assessments performed in New York State psychiatric facilities as part of the evaluation of the state's clozapine program. Using regression analysis, they noted that improvement in the hostility subscale was over and above that of the psychosis factor—suggestive of a selective effect. Buckley and colleagues³⁸ observed significant reductions in seclusion and restraint in aggressive patients with schizophrenia (pre-clozapine mean of 100.4 hours, mean of 37.9 hours at 6 months of clozapine therapy), yet the overall response on the BPRS in these patients was comparable to that of nonaggressive patients, suggesting that the amelioration of aggressive symptoms was not coupled to a preferential antipsychotic response in violent patients. Rabinowitz and colleagues⁴⁰ reported efficacy for clozapine in managing schizophrenic patients with aggression. They showed a weak relationship between the BPRS psychosis factor and changes in hostility score, lending further credence to the notion that clozapine may have a se-

lective antiaggressive effect. The recently published Patient Outcomes Research Team (PORT) treatment guidelines recommend consideration of clozapine therapy for schizophrenic patients with persistent aggression.⁴² Clozapine has also been shown to reduce aggression in nonpsychotic conditions, such as borderline personality disorder.²⁹

Risperidone. Czobor and colleagues,⁴³ in a subanalysis of the U.S. multicenter comparative trial between risperidone and haloperidol, noted a superior effect of risperidone in aggression/agitation in this sample. In a state hospital population, Buckley and colleagues⁴⁴ noted that risperidone was as efficacious as conventional neuroleptics in ameliorating aggression in schizophrenic patients. Another study, by Chengappa and colleagues⁴⁵ at Mayview State Hospital, noted a significant decline in seclusion and restraint in a pretreatment/posttreatment comparison among patients receiving risperidone. Recently, a large multicenter study of risperidone in the treatment of behavioral disturbance in dementia reported favorable reductions in agitation and good tolerability at a 1-mg dose of risperidone.³⁰ Risperidone has also been shown in a recent placebo-controlled study to be effective in controlling agitation in adult autistic patients.⁴⁶

It should be noted that the availability of risperidone in liquid form is an advantage in choosing among drugs for acute management of agitation. However, as is the case for all of the novel antipsychotics, there is currently no short-acting intramuscular preparation. The first of the newer drugs to be produced in this form will most likely result in its preferential use for the management of aggression. Conversely, the availability of typical antipsychotics in intramuscular form retains their primacy in acute management of aggression.

Olanzapine. Olanzapine is a novel antipsychotic with demonstrated superiority over haloperidol in the treatment of positive, negative, and depressive symptoms in schizophrenia.⁴⁷ There are, as yet, no published data on the use of olanzapine in patients with persistent aggression. However, an analysis of the multicenter clinical trials of olanzapine shows equal efficacy between olanzapine and haloperidol in treating agitation and/or aggression.⁴⁸ There are also some preliminary data to suggest that olanzapine may be helpful and well tolerated in treating elderly schizophrenic patients.⁴⁹

Quetiapine. Quetiapine is another novel antipsychotic that has been shown to be as efficacious as haloperidol and to possess a benign extrapyramidal symptom (EPS) side effect profile.⁵⁰ There are, as yet, no published data on the efficacy of quetiapine in patients with persistent aggression. An analysis of the multicenter trials of quetiapine showed some evidence of a selective effect upon hostility that was not observed with haloperidol.⁵¹

Other novel antipsychotic medications. Sertindole, another atypical agent with efficacy in the treatment of schizophrenia,⁵² was shown to reduce agitation in a case

series of psychotic patients.⁵³ However, no other data are available and this drug is currently in use only in Europe. Ziprasidone, currently under review by the United States Food and Drug Administration (FDA), has been prepared in a short-acting intramuscular form that appears to be well-tolerated.⁵⁴ This drug is not available for clinical practice. However, available information on its efficacy is encouraging.⁵⁵ Zotepine is another novel agent, not available in the United States but recently approved for use in several European countries, that has been shown to be superior to conventional antipsychotics in treating positive and negative symptoms of schizophrenia.⁵⁶ It has been noted to be more efficacious than either haloperidol or thiothixene in BPRS-derived measures of hostility and activation.⁵⁶

Loxapine: Old Is New?

The greater propensity to block serotonin (5-HT₂) receptors in tandem with relatively low dopamine (D₂) receptor antagonism has been postulated as one defining characteristic of "atypicality" among novel antipsychotic medications.⁵⁷ Moreover, this pharmacologic dualism is considered important in conferring the more benign extrapyramidal side effect profile that has been observed with these newer drugs. However, as has been well demonstrated with the dosage refinements of risperidone in clinical practice,⁵⁸ this is not an all-or-none phenomenon, and at higher doses some of the novel antipsychotics show rates of EPS that (while still lower than conventional antipsychotics) are substantial. Recent studies of 5-HT₂ and D₂ receptor occupancy using positron emission tomography (PET) confirm the importance of dose as a dimension when considering the atypicality of novel antipsychotic medications.^{59,60} Kapur and colleagues⁶⁰ have reported that even at a 5-mg daily dose of olanzapine, the occupancy of central 5-HT₂ receptors is almost saturated. In contrast, 43% to 80% D₂ receptor occupancy is achieved within a 5 to 20 mg dosing range. When olanzapine is prescribed at a daily dose of 30 to 40 mg, the D₂ receptor occupancy rates are 83% to 88%.

In this context, there is renewed interest in loxapine, an older antipsychotic agent that is chemically distinct from phenothiazines, butyrophenones, and thioxanthenes. More recent research suggests that this agent has a 5-HT₂/D₂ occupancy ratio that is more characteristic of the atypical antipsychotics than the typical medications.⁶¹⁻⁶³ In vitro binding data suggest that 5-HT₂ receptor occupancy of loxapine exceeds that of D₂ receptors.⁶¹ In vivo PET data suggest comparable 5-HT₂ and D₂ binding when moderate doses of loxapine are prescribed.⁶³ Kapur and colleagues⁶³ reported a range of D₂ occupancy between 43% and 90% and 5-HT₂ occupancy between 27% and 98% in 10 patients with schizophrenia who were receiving loxapine (dose range, 10-100 mg/day). Dose occupancy curves for D₂ and 5-HT₂ were indistinguishable. These results sug-

gest that loxapine is relatively equipotent for each receptor. One patient who was receiving loxapine, 20 mg daily, had 71% D₂ occupancy and 58% 5-HT₂ receptor occupancy. It would appear from these data that loxapine in doses of 20 to 40 mg (or perhaps lower) might maximize the dual 5-HT₂/D₂ antagonism. This dose may be efficacious and, in particular, may have a lower risk of EPS than the chlorpromazine-equivalent dose of another typical antipsychotic. This speculation needs to be confirmed or refuted through clinical research. This point is also of particular relevance to the issue of aggression because (like for the typical drugs) high doses of loxapine are generally used to treat these patients.

It is also noteworthy from the viewpoint of acute management of aggression that the short-acting intramuscular form of loxapine is more likely to achieve higher 5-HT₂ saturation than oral loxapine. Intramuscular delivery of loxapine avoids degradation of loxapine to its metabolite hydroxyloxapine, the latter being a potent D₂ antagonist.⁶²

Although there have been no recent studies of loxapine's efficacy in managing aggression, several comparative studies between loxapine and other antipsychotics have specifically addressed this topic.⁶⁴⁻⁶⁹ Moreover, most of these studies were conducted in state hospital populations in which aggression is a significant clinical dilemma. In a study at Norristown State Hospital, Moyano⁶⁴ compared the efficacy of loxapine (mean dose unspecified; dose range, 20-40 mg daily) and trifluoperazine in 49 patients with schizophrenia. Loxapine proved superior to trifluoperazine across a range of BPRS items, including hostility. At a Texas state hospital, Selman and colleagues⁶⁵ conducted a 12-week, placebo-controlled trial of loxapine and haloperidol in 79 patients with schizophrenia. Loxapine and haloperidol were equally efficacious and superior to placebo on BPRS measures of irritability, but loxapine alone proved statistically superior on the irritability item of the Nurses Observation Scale for Inpatient Evaluation. Paprocki and Versiani⁶⁶ reported a comparative study in 35 acutely ill schizophrenic patients between loxapine (mean total daily dose = 115 mg) and haloperidol (11 mg) given intramuscularly over a 4-day study period. Loxapine-treated patients showed less agitation and aggressive behavior. The authors concluded that "loxapine is an agent which can be safely employed in the management of aggressiveness and overtly disturbed behavior in acute psychotic patients."^{66(p80)} Ereshefsky and colleagues⁶⁷ at San Antonio State Hospital reported that loxapine in large doses (range, 50-400 mg) was effective for treating psychosis and aggressive behavior in a sample of neuroleptic-refractory patients with chronic schizophrenia. A more recent case series of patients who had persistent symptoms despite adequate clozapine monotherapy reported a dramatic cessation of aggressive behavior when loxapine was given adjunctively in 2 patients.⁶⁸ Finally, a double-blind study of loxapine (mean daily dose = 36 mg) versus haloperidol (7 mg) in 40 de-

mentia patients (mean age = 79 years) showed comparable reduction in aggression (mean aggression score change = 4.4 for loxapine vs. 3.5 for haloperidol).⁶⁹ Loxapine was better tolerated than haloperidol. It would be helpful, given the issues of atypicality of receptor affinity, to examine loxapine's efficacy in managing aggression at doses below 30 mg daily and to do so in direct comparison with either haloperidol or a novel antipsychotic.

Other Psychotropic Drugs

Lithium has been reported to have an antiaggressive effect, especially in mental retardation and prison inmate populations.^{25,70} However, this agent is no longer considered as the primary augmentation treatment in schizophrenia.⁷¹ Similarly, carbamazepine has been shown in earlier studies to be helpful in patients with schizophrenia who have persistent aggression.⁷² There are no recent studies of carbamazepine's efficacy in aggression, and its role as an augmentation agent is unclear,⁷¹ particularly since it is contraindicated for coadministration with clozapine. Valproate has also been shown to be effective in aggression.⁷³ The role of mood stabilizers in managing aggression is most evident where agitation and/or aggression is due to an underlying affective disorder. Aggression may persist due to uncontrollable affective symptoms. In this regard, there is preliminary evidence that lamotrigine, a novel anticonvulsant, is helpful in refractory mania.⁷⁴

β-Blockers have been proposed as a treatment approach for persistent aggression.^{24,70,75} In a study of 17 weeks' duration in 41 patients with chronic psychoses, nadolol (at a modal dose of 120 mg daily) given as adjunctive therapy with a typical antipsychotic medication (mean dose = 1173 mg daily) resulted in fewer episodes of aggressive behavior and fewer p.r.n. medications than with neuroleptic monotherapy.⁷⁵ However, it is the experience of many clinicians that the high doses of the β-blockers required often result in problematic side effects of sedation and postural hypotension.

Benzodiazepines are also a mainstay of the treatment of aggression.^{24,76} Short-acting agents, such as lorazepam, have a rapid onset of calming effect that lasts for several hours. Moreover, many of these agents are available in tablet, liquid, and intramuscular preparations. Lorazepam is a frequent choice. It has no active metabolites and is not metabolized by the liver. The main drawback to the use of benzodiazepines is that they are not helpful in persistent aggression, wherein long-term use may result in pharmacologic tolerance, delirium, cognitive impairments, respiratory depression, and even the potential for paradoxical aggression. Short-term disadvantages include excessive sedation, memory impairment, and respiratory depression. These effects are particularly liable to occur in elderly patients.

Antidepressant medications, particularly selective serotonin reuptake inhibitors (SSRIs), have been used to

treat pathologic aggression.^{24,77} Their effect has been best demonstrated in impulsivity when it occurs as a consequence of personality disturbance or of traumatic brain injury.^{78,79}

Treating Aggression: Which Drug and When?

Although some specific drugs and drug classes appear to be more advantageous than others in ameliorating aggression in psychiatric inpatients, there is as yet no agent with an FDA-established indication for this symptom. Desirable characteristics of a drug for the treatment of aggression are listed in Table 3. Additionally, because aggression occurs in a wide variety of primary psychiatric and neuropsychiatric conditions, the rationale for choosing one agent over another will differ between these circumstances. For example, when aggression is a concomitant of a manic episode, then targeted treatment for mood stabilization (e.g., lithium, anticonvulsants) is the primary pharmacologic approach. Acute management may be augmented with short-term use of benzodiazepines or neuroleptics, either typical or atypical. Where aggression persists because of refractory mania, then a novel mood-stabilizing agent or neuroleptics may be tried. In this instance, novel antipsychotics should be considered because of both their low propensity to induce tardive dyskinesia and their mood-stabilization effects. Neuroleptics are the treatment of choice for agitation in demented patients.⁸⁰ Low doses are recommended, and treatment should proceed slowly with gradual titration of dose. Typical antipsychotics are still more frequently prescribed, although risperidone and olanzapine are being increasingly used in nursing homes. A favorable EPS profile of loxapine in low doses in tandem with availability of intramuscular formulation for crisis management may offer an advantage in this patient group. Benzodiazepines should be used with caution and sparingly because of the high toxicity in this patient group. The relative role of various psychotropics in managing aggression in distinct diagnostic groups is covered in detail elsewhere.²⁴

The issue of acute versus chronic behavioral disturbance is critical to considering the choice of medication for aggression. In general hospitals and in most private psychiatric facilities, aggressive behavior among inpatients is most often an acute-phase phenomenon as a result of altered mental status (e.g., substance abuse, intoxication, infection, metabolic disturbance) or hyperarousal from mania or from schizophrenic psychosis. In such instances, once the assessment has indicated that there is a need for acute pharmacologic intervention, benzodiazepines and typical and atypical antipsychotics should be considered as drugs of choice for treating aggression. Short-term management currently favors the typical antipsychotics—especially mid-potency to high-potency agents—because of their efficacy, ease of use and titration (e.g., ability to use p.r.n. dosing, lower liability to induce

Table 3. Desirable Characteristics of a Drug to Treat Aggression

Selective antiaggressive effect
Antiaggressive effect in a broad spectrum, ie, efficacy across different patient groups and pathologies
Availability in oral (tablet and liquid) and intramuscular (short-acting and long-acting) forms
Rapid onset of action
Low toxicity
Low potential for drug-drug interactions

hypotension) and, most particularly, their availability in tablet, liquid, and intramuscular forms. Haloperidol, fluphenazine, and loxapine are good choices for short-term management. Loxapine has a close homology to clozapine in receptor affinity (likely to be even more pronounced when loxapine is administered intramuscularly) and in earlier studies (see above) showed superiority over other typical antipsychotics in treating aggression. When used in low doses, loxapine is less likely to induce EPS. Among the novel antipsychotics, risperidone (which is available in tablet and liquid forms) and olanzapine merit consideration. These latter agents may be particularly beneficial in elderly patients.

The pharmacologic management of persistent aggression is more complex. In neuropsychiatric conditions (e.g., dementia, head trauma), aggression may be a long-term consequence of brain damage and thereupon less amenable to treatment. For mood states and schizophrenia, persistent aggression is often a behavioral consequence of refractory or inadequately treated illness. Maximizing control of the underlying psychiatric illness by the most appropriate medication for that condition should be the primary target. Typical antipsychotics, while effective in acute management of aggression, are less advantageous as a primary choice in persistent aggression because of the long-term risk of tardive dyskinesia and the lack of effect in refractory schizophrenic patients. However, they may have a specific role in augmentation when the atypical agent has failed to adequately control aggressive symptoms.⁶⁸ Additionally, the long-acting depot intramuscular form of a typical antipsychotic should be considered when aggression persists because of chronic medication non-compliance.⁸¹ In the other circumstance, in which acute management is required for the patient who is refusing to take a novel antipsychotic, then a typical agent is an appropriate choice. Loxapine is a useful option here, even as an acute stabilization strategy and transition to subsequent use of an atypical agent.

That apart, atypical antipsychotics should be considered the drugs of choice for persistent aggression. Specifically, clozapine has been recommended for persistent aggression in psychosis.⁴² Additionally, clozapine appears to have a selective antiaggressive effect above and beyond the control of psychosis. Data thus far for risperidone and olanzapine are also encouraging. Moreover, although

these agents may differ between each other in their long-term liability to induce tardive dyskinesia, available data confirm that the risk of tardive dyskinesia is much lower with these novel antipsychotics. Since organic brain damage is a known risk factor for tardive dyskinesia, selecting clozapine or another new drug for managing persistent aggression in neuropsychiatric conditions will minimize the likelihood of this outcome.

There is now a growing appreciation that changing antipsychotics, especially among newer drugs, is complicated and poses a risk of relapse.⁸² This risk is magnified when aggression may be a consequence of deterioration. Accordingly, careful cross-titration of antipsychotic medications is particularly important in these patients. This should be done gradually with small incremental changes in doses of medication.⁸³ However, since it is speculated that the profile of receptor affinity of atypical medication is of relevance to treating aggression, it is important that clinicians give an adequate trial of monotherapy once treatment has begun.

TREATMENT RECOMMENDATIONS

The following are some specific recommendations on the management of aggression:

- Ensure an adequate assessment in advance of treatment. Rule out substance abuse and/or intoxication and other medical conditions. Clarify the primary diagnosis.
- Ensure adequate protection for other patients and staff (e.g., avoid direct confrontation, avoid unit overcrowding).
- Ensure adequate hydration and promote good sleep hygiene.
- Use the lowest effective dose of medication, with regular reassessment of efficacy and side effects.
- Avoid high doses of neuroleptics.
- Avoid polypharmacy.
- Consider benzodiazepines or neuroleptics (e.g., loxapine, haloperidol, quetiapine, risperidone, or olanzapine) for acute aggression.
- Consider atypical antipsychotics (e.g., clozapine, quetiapine, risperidone, or olanzapine) for persistent aggression.

SUMMARY

Aggression among persons with serious mental illness occurs relatively infrequently, yet it is clearly a significant problem. To date, pharmacologic approaches have been unclear and inconsistent. In tandem with the advances in the psychopharmacology of psychosis, a reconsideration of the role of each drug class in the management of aggression is timely. Typical antipsychotics continue to have a

primary role in acute management in psychosis and in long-term management where noncompliance necessitates the use of long-acting depot neuroleptic preparations. On the other hand, persistent aggression in psychosis should be managed by atypical antipsychotics with a preferential indication for clozapine, for which the most data on efficacy are available. Further refinement of the treatment of aggression and the development of specific algorithms would be greatly advanced by comparative studies between antipsychotic medications in this patient population. Given the significance of this issue, such research in this population is long overdue.

Drug names: carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril), fluphenazine (Prolixin and others), haloperidol (Haldol and others), lamotrigine (Lamictal), lorazepam (Ativan and others), loxapine (Loxitane and others), nadolol (Corgard), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane), trifluoperazine (Stelazine).

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