The Psychopharmacology of Violence With Emphasis on Schizophrenia, Part 2: Long-Term Treatment

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In last month's column we reviewed the short-term approaches in treating agitation. Once the acute episode of agitation is managed, however, the clinician is left with the task of reducing the frequency and intensity of future episodes. This month's column will review the long-term management of aggressive behavior in schizophrenia.

Treatment Considerations

As is the case during acute treatment, behavioral interventions may be helpful, but the foundation for control of persistent aggressive behavior in patients with schizophrenia is medication treatment. Sedation alone is inadequate and, in fact, impedes the patient from reintegrating into the community. Establishing the root cause(s) for the behavior is helpful for determining what type of medication is most appropriate. Is the behavior related to positive psychotic symptoms? If so, an antipsychotic for better control of hallucinations and delusions would be necessary for improvement. Is the patient impulsive? Then perhaps an anticonvulsant in addition to an antipsychotic may be helpful. Other considerations include whether or not the patient is abusing alcohol or substances, has antisocial personality traits, or is stressed by a chaotic environment, all of which can contribute to aggressive behavior. Unfortunately, there is very little in the way of controlled clinical trials that support our medication options for treatment of persistent aggressive behavior, but so far the strongest evidence is for the use of clozapine.[1]

Evidence

Clozapine. In a prospective controlled study funded by the National Institute of Mental Health (NIMH),[2] clozapine was shown to reduce Positive and Negative Syndrome Scale hostility item scores in 157 patients with treatment-resistant schizophrenia who were randomly assigned to receive double-blind clozapine (mean dose: 402 mg/day at week 8, and 527 mg/day at week 14) versus olanzapine (mean dose: 19.6 mg/day at week 8, and 30.4 mg/day at week 14), risperidone (mean dose: 7.9 mg/day at week 8, and 11.6 mg/day at week 14), or haloperidol (mean dose: 18.9 mg/day at week 8, and 25.7 mg/day at week 14) for up to 14 weeks.

This antihostility effect was specific in that it was independent of clozapine's effect on other positive symptoms and independent of sedation or akathisia. The effect was statistically superior to that observed with risperidone or haloperidol (but not to olanzapine) and was supported by another analysis[3] from the same study demonstrating a decrease in actual aggressive acts in the clozapine group as measured by the Overt Aggression Scale.[4] However, this study enrolled patients who were not necessarily aggressive, which limits its generalizability.

To address this limitation, another NIMH-funded study was undertaken that enrolled 110 patients who had been physically aggressive and subsequently randomly assigned to receive double-blind clozapine (mean dose: 457 mg/day at week 6, and 566 mg/day at week 12), olanzapine (mean dose: 19.8 mg/day at week 6, and 24.7 mg/day at week 12), or haloperidol (mean dose: 19.6 mg/day at week 6, and 23.3 mg/day at week 12) for up to 12 weeks.[5] Patients assigned to clozapine had statistically significant lower endpoint aggression scores than patients assigned to either olanzapine or haloperidol. Patients in the olanzapine group had statistically significant lower endpoint aggression scores than patients in the haloperidol group. No differences were seen among the 3 groups in terms of reduction of psychopathology as measured by the total Positive and Negative Syndrome Scale score.

Other second-generation antipsychotics. Post hoc analyses of randomized clinical trial data have been reported for patients enrolled in comparisons of risperidone versus haloperidol,[6] olanzapine versus haloperidol,[7] quetiapine versus haloperidol,[8] aripiprazole versus haloperidol,[9] and ziprasidone versus haloperidol.[10] Results varied from superiority[6–8,10] to equivalency to haloperidol[9] in terms of antihostility or antiaggressive effect. Compared with haloperidol, the second-generation antipsychotics were associated with fewer extrapyramidal effects and, hence, were considered more tolerable and thus overall more effective. Methodologies varied, however, and specific antihostility or antiaggressive effect was not always determined[7] or inconsistently demonstrated.[8,11] All of these post hoc analyses used data from clinical trials that did not specifically enroll aggressive patients and, in fact, may have selected against the more severely disturbed patients from participating, rendering generalizability more difficult.[12] Conflicting systematic observations that do not support an efficacy advantage for a superior antiaggressive effect for risperidone also exist.[13,14]

Mood stabilizers. Adjunctive valproate has been used to decrease aggression,[15] perhaps explaining the high utilization rate of about 35% among patients with schizophrenia hospitalized for intermediate and long-term care in New York State psychiatric centers.[16] Data for this specific indication for valproate and other mood stabilizers are shallow, consisting principally of small studies or uncontrolled observations.[17,18] However, a selective antihostility effect for valproate was demonstrated for the first week of a 4-week randomized clinical trial comparing risperidone or olanzapine monotherapy versus risperidone or olanzapine combined with valproate.[19] The same caveats for the post hoc analyses of antipsychotics also apply here.

To date there has not been a reported double-blind randomized clinical trial examining the adjunctive use of anticonvulsants in patients with schizophrenia selected specifically for persistent aggressive behavior, whatever the root cause of this behavior may be. A significant methodological obstacle to the conduct of these studies would be the systematic exclusion of the most severely ill patients, who are often unable to undergo an informed consent process.

β-Adrenergic blockers. The utility of adjunctive β-adrenergic blockers for aggressive behavior has been known for quite some time, and double-blind clinical trials have been undertaken.[20,21] The disadvantages found were that onset of action may be delayed and dose-limiting hypotension and bradycardia may develop.[21]

Selective serotonin reuptake inhibitors. Selective serotonin reuptake inhibitors have also been hypothesized to decrease aggression, and this hypothesis is supported by a double-blind randomized clinical trial of adjunctive citalopram in patients with chronic schizophrenia.[22]

Benzodiazepines. The use of benzodiazepines, although helpful for acute treatment, may be harmful in the long run for some patients. Missing scheduled doses of lorazepam may, for example, result in withdrawal symptoms that can contribute to agitation or excitement as well as irritability and a greater risk for aggressive behavior. A double-blind, placebo-controlled trial of adjunctive clo-

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nazepam in 13 patients with schizophrenia resulted in no additional therapeutic benefit, with 4 patients demonstrating violent behavior during the course of treatment with clonazepam.[23]

Considering all information presented, for the patient with schizophrenia and persistent aggressive behavior, the evidence points to clozapine as the best long-term medication choice, followed by other second-generation antipsychotics.[5] Clozapine is not an "acute" medication because the dose must be titrated slowly during the first 3 weeks or so of treatment. Although often used, adjunctive anticonvulsants have not been adequately studied under controlled conditions for this indication in patients with schizophrenia, although if we extrapolate from studies measuring impulsivity in other disease states,[24] this may help justify the selective use of this agent on a case-by-case basis.

Summary

Effectively managing aggression and violence is important not only to assure safety, but also to improve functional outcomes. The multidimensional etiology of the behavior complicates treatment. The clinician has to effectively treat any underlying psychosis, poor impulse control, and comorbid substance use and understand how any personality traits that the patient may have contribute to the maladaptive behavior. Complicated medication regimens are often used, and a rational approach involves considering the available research evidence, tempered by the individual's history of response, and often includes sequential and careful time-limited empirical "N = 1" medication trials.

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