Underlying Mechanisms of Psychosis and Aggression in Patients With Alzheimer's Disease

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It is well known that serotonergic function is related to aggression. Patients with Alzheimer's disease exhibit aggressive behavior, and alterations in their serotonergic function have been identified. Recent clinical trials involving new antipsychotic agents, such as risperidone, which has both serotonergic and dopaminergic activity, have demonstrated the efficacy and safety of these drugs in treating the psychosis and aggressive behavior associated with dementia.

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The etiology of psychosis and aggression in Alzheimer's disease is not well defined. To date, deficits in dopamine activity have been linked to psychosis in both Alzheimer's disease and schizophrenia.[1] Conventional neuroleptic drugs with dopaminergic activity have been the mainstays of therapy. However, more recent research suggests that the dopamine hypothesis may be only part of the puzzle. Specifically, these findings suggest that deficits in the serotonergic[2,3] and cholinergic systems are associated with both psychosis and aggression in Alzheimer's disease. The development of antipsychotic drugs with serotonergic function may have strong therapeutic implications. In this article, recent data from clinical trials involving the new antipsychotic agent risperidone and their implications for the future treatment of psychosis and depression in Alzheimer's disease are discussed.

CONVENTIONAL NEUROLEPTICS IN THE TREATMENT OF PSYCHOSIS AND AGGRESSION

Recent clinical trials have indicated that conventional neuroleptic drugs have little value in controlling the behavioral and psychological symptoms of dementia (BPSD), particularly aggression. A randomized trial by Devanand et al.,[4] for example, assessed the efficacy of haloperidol in treating patients with Alzheimer's disease and disruptive or psychotic behaviors. Over a 6-week period, 71 patients received placebo or haloperidol (0.5–0.75 mg/day or 2–3 mg/day). The results showed that haloperidol, 0.5–0.75 mg/day, was no more effective than placebo. At the higher dose of 2 to 3 mg/day, the drug significantly improved symptoms of psychosis ($p < .03$) and psychomotor agitation ($p < .04$) when compared with placebo. Unfortunately, 25% of these patients experienced a substantial increase in extrapyramidal side effects (EPS) and cognitive impairment. Neither drug regimen induced statistically significant differences from placebo with respect to physical aggression and hostile-suspiciousness.

Conventional neuroleptics are, therefore, not indicated for aggression, and their effectiveness in treating psychosis is counteracted by a high incidence of side effects. To achieve optimal pharmacologic control of BPSD, it is necessary to use drugs that could rectify the underlying physiologic dysfunction such as a serotonergic deficit.

SEROTONIN AND AGGRESSION

It has been known for some time that serotonergic function is related to aggression. Initially, Yen et al.[5] observed that reduced levels of serotonin (5-HT) made mice more aggressive. Similarly, low levels of serotonin have been associated with violent behavior and suicide in depressed patients. Furthermore, aggressive patients with personality disorder show a lack of prolactin response to challenge with fenfluramine, a serotonin-releasing/uptake-inhibiting agent.[6] These results suggest that such patients have a reduced central serotonergic function.

Alterations in serotonergic function have also been identified in patients with Alzheimer's disease. The disease

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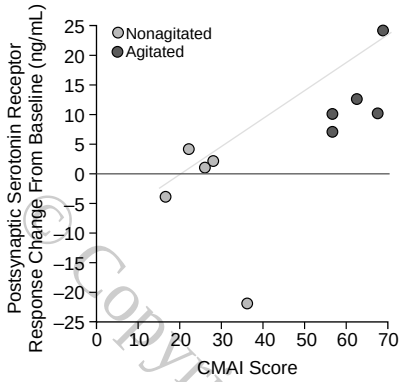
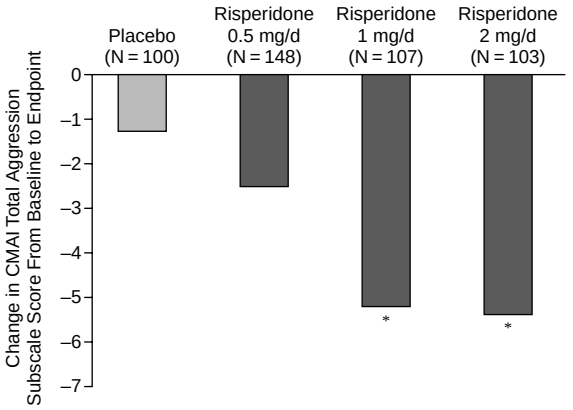
Figure 1. Correlation Between Postsynaptic Serotonin Receptor Response and Total Cohen-Mansfield Agitation Inventory (CMAI) Score[a,b]



[a]Reprinted with permission from Mintzer et al.[10]
[b]r = .74, p = .01.

Figure 2. Effect of Risperidone on Aggressive Behavior in Patients With Dementia[a]



[a]Data from Katz et al.[11] Abbreviation: CMAI = Cohen-Mansfield Agitation Inventory.
*p < .05 vs. placebo.

may be associated with reduced levels of 5-HT metabolites in cerebrospinal fluid.[7,8] Additionally, cell loss and tangle formation in the raphe nucleus and loss of 5-HT_1 and 5-HT_2 receptors have been reported.[9]

Many Alzheimer's disease patients exhibit aggressive behavior. My colleagues and I[10] hypothesized that it was these patients who had impaired serotonergic function. We examined serotonin levels in patients with Alzheimer's disease who were aggressive and compared them with levels in nonaggressive patients. The results showed that the most aggressive patients had the highest deficits in serotonin and vice versa (Figure 1). Thus, a medication that acts on the serotonin system should have effects on aggression.

RISPERIDONE AND OTHER ATYPICAL ANTIPSYCHOTICS IN THE TREATMENT OF PSYCHOSIS AND AGGRESSIVE BEHAVIOR

The atypical antipsychotic risperidone has both serotonergic and dopaminergic activity. The efficacy of this drug in controlling psychosis and aggressive behavior has been evaluated in a number of clinical trials.

A 12-week, randomized, multicenter trial[11] compared risperidone with placebo. The study recruited 625 patients, 73% of whom had Alzheimer's disease, 16% had vascular dementia, and 11% had mixed dementia. Their mean age was 83 ± 8 years, and 43% were women. Since risperidone retains its serotonergic activity at lower doses, it was postulated that doses of 2 mg/day or less could be sufficient to control aggressive behavior. Patients were therefore randomly assigned to receive risperidone, 0.5, 1, or 2 mg/day, or placebo.

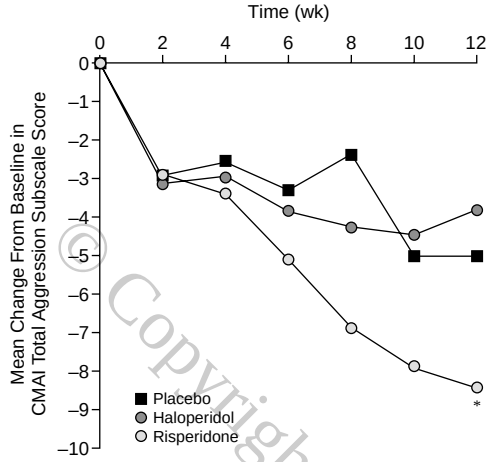
The results were compared using the Behavior Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) and the Cohen-Mansfield Agitation Inventory (CMAI). At doses of 1 or 2 mg/day, risperidone caused a significantly greater improvement than placebo ($p < .05$) in the BEHAVE-AD psychosis score. The same dosage regimens also induced a significant improvement in BEHAVE-AD aggressiveness score when compared with placebo ($p < .05$). These results were mirrored in the CMAI total aggression subscale, a more reliable measure of aggressive behavior. Again, a dose of 1 or 2 mg/day of risperidone was significantly more effective than placebo ($p < .05$) in controlling aggression (Figure 2).

What price do we have to pay for this efficacy? Overall, risperidone was well tolerated, and a difference from placebo in the incidence of EPS was apparent only at the 2-mg dose. When compared with placebo, the 2-mg regimen was also associated with an increased incidence of other adverse events, including somnolence and peripheral edema, although significance was not reached. A 1-mg daily dose of risperidone was judged to be the most efficacious regimen for the treatment of aggression.

The effectiveness of this serotonin-oriented approach to aggression therapy has also been shown in relation to conventional neuroleptic drugs. A large clinical trial[12] involving 344 elderly patients with dementia compared risperidone with haloperidol, a conventional neuroleptic with no serotonergic action. Over 13 weeks, patients received either placebo or variable doses of risperidone or haloperidol (0.5–4 mg/day). The mean doses of risperidone and haloperidol at 13 weeks were 1.1 and 1.2 mg/day, respectively.

Analysis using the BEHAVE-AD aggressiveness score found that risperidone was more effective against aggression than were placebo ($p < .01$) or haloperidol ($p = .05$). These findings were corroborated by CMAI total aggression subscale analysis, in which the advantage of risperi-

Figure 3. Comparison of Risperidone With Haloperidol and Placebo for the Treatment of Aggression[a]



[a]Reproduced with permission from De Deyn et al.[12]
Abbreviation: CMAI = Cohen-Mansfield Agitation Inventory.
*p = .01 vs. placebo; p = .02 vs. haloperidol.

done over placebo and haloperidol was more pronounced (Figure 3). Haloperidol was more effective than placebo against aggression according to both indices ($p < .01$). However, these patients may have been less aggressive as a result of haloperidol-induced sleepiness and EPS, both of which are undesirable clinical outcomes. In contrast, improvements in the behavior of patients receiving risperidone can be attributed to the serotonin activity of the drug, as they were not accompanied by concomitant increases in sleepiness or EPS. Furthermore, the risk of tardive dyskinesia due to risperidone is low. In separate, placebo-controlled studies, Jeste et al. quantified the incidence of tardive dyskinesia among patients receiving conventional neuroleptics[13] or risperidone.[14] The 1-year incidence of persistent tardive dyskinesia was 2.6% for patients receiving risperidone and 26% in the conventional neuroleptic group. These findings suggest that conventional neuroleptics are associated with a 10-fold higher rate of tardive dyskinesia than is risperidone.

Similarly, Street and coworkers[15] reported on the efficacy of olanzapine in the treatment of psychosis and aggression in Alzheimer's disease patients. Patients were evaluated using the core total of the Neuropsychiatric Inventory (NPI) (nursing home version), and olanzapine was reported to be most effective in controlling these symptoms when given at low dose, i.e., 5 mg/day. Improvements in NPI core total were not significantly different from placebo for patients receiving olanzapine at 15 mg/day. It is interesting to note that the low dose range in which olanzapine and other atypical antipsychotics are most efficacious in treating psychosis and aggression matches the dose range at which they exert their maximal effect on serotonin activity.

FUTURE CHALLENGES

Although our knowledge of antipsychotic drugs is growing, we still have much to learn. For example, it appears that the cholinergic and serotonergic neurotransmitter systems are significantly impaired in Alzheimer's disease. The interaction between these systems is extremely complex, and so if we intervene pharmacologically, the effects are widespread and difficult to predict. Our challenge, therefore, is to obtain a greater understanding of these systems and how we can use drugs to influence them for the benefit of patients.

Drug names: haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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