Atypical Antipsychotic Agents in the Treatment of Schizophrenia and Other Psychiatric Disorders

Part I: Unique Patient Populations

This 2-part ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents highlights from 3 symposia held at the 150th Annual Meeting of the American Psychiatric Association, San Diego, California, May 17–22, 1997, and sponsored by Janssen Research Foundation, Titusville, New Jersey. The second part of this series, highlighting special considerations of antipsychotic use, will appear in the June 1998 issue.*

The chair of the first symposium, "Antipsychotics in Unique Patient Populations," was Stephen R. Marder, M.D., Professor and Vice Chair, Department of Psychiatry, UCLA School of Medicine, Los Angeles, California. The chair of the second symposium, "Psychiatric Management of Long-Term Care Patients," was Dilip V. Jeste, M.D., Director, Geriatric Psychiatry Clinical Research Center, University of California, San Diego, and V.A. Medical Center, San Diego, California. The chair of the third symposium, "Challenge: Making the Most of Therapy With Atypical Antipsychotics," was Joseph P. McEvoy, M.D., Associate Professor, Department of Psychiatry, Duke University, Durham, North Carolina.

Participants in the symposia are listed at the end of each part of this 2-part series.

Antipsychotics in Treatment-Refractory Schizophrenia

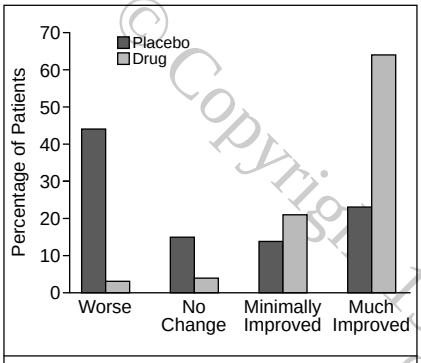
A large proportion of patients with schizophrenia fail to respond adequately to their medications and can be considered as treatment-refractory, Dr. Stephen R. Marder declared. The advent of newer atypical antipsychotics requires an expanded definition of treatment refractoriness and more thoughtful application of treatment alternatives to the traditional dopamine receptor antagonists. In this context, Dr. Marder discussed positive symptoms and broadened the definition of patients who could be considered treatment-refractory. He discussed the increased efficacy and tolerability of the newer antipsychotics and suggested their uses in treatment-refractory patients.

The increased efficacy and tolerability of newer antipsychotics require revision of conventional attitudes toward treatment-refractory patients with schizophrenia. Dr. Marder noted that, traditionally, assessment of treatment-refractoriness focused on seriously ill, hospitalized patients with refractory positive symptoms—hallucinations, delusions, or thought disturbances that responded poorly to antipsychotics. However, patients with schizophrenia also experience refractory negative symptoms (affective flattening, alogia, anhedonia-asociality, inattention) and neurocognitive symptoms that can be equally disturbing. Perhaps insufficient treatment of the latter (negative and neurocognitive symptoms) is even more disturbing to patients because they are likely to occur in the community setting where they can influence both social and vocational adjustment. Other patients who could be considered treatment refractory are those intolerant to antipsychotic medications, including traditional neuroleptics. All refractory patients should be reassessed as possible candidates for the newer antipsychotics, according to Dr. Marder.

Older studies of refractoriness may not have presented the total picture of patients' and families' dissatisfaction with clinical response to traditional neuroleptics. Placebo-controlled studies conducted in the 1960s with older antipsychotics showed that more than 60% of schizophrenic patients showed much improvement, but that means that close to 40% did not (Figure 1).[1,2] Using a newer, broader definition of treatment refractoriness and queries of patients and their families might have shown that more than 50% were dissatisfied with the clinical response to traditional neuroleptics. Dr. Marder noted that lack of clinical response is only 1 reason conventional neuroleptics are probably some of the most detested therapies in psychiatry.

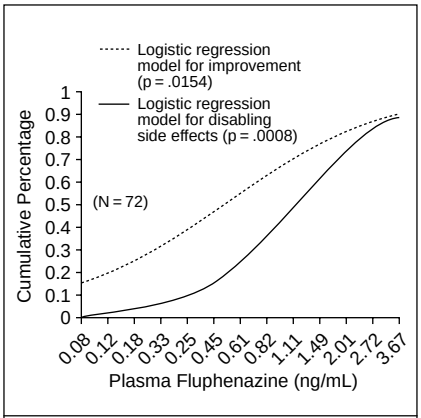
Results of a 1991 study[3] showed that increased plasma drug levels were associated not only with an increase in clinical response but also with an increase in serious, disabling side effects (Figure 2). At a plasma level of 0.60 ng/mL (approximately 10 mg of fluphenazine), 60% of patients were sub-

Figure 1. Treatment Outcomes in Patients With Schizophrenia Treated With a Conventional Neuroleptic or Placebo in Trials Conducted During the 1960s*



*Data from National Institute of Mental Health[1] and Janicak et al.[2]

Figure 2. Improvement and Disabling Side Effects as a Function of Plasma Fluphenazine Levels*



*Reprinted with permission from van Putten et al.[3]

stantially improved, but close to the same proportion of patients experienced side effects so serious that any reasonable clinician would have lowered the dose or changed treatment.

Dr. Marder proposed that treatment resistance did not really become a research issue until publication of the clozapine multicenter study by Kane et al. in 1988.[4] In this study, a group of floridly psychotic, treatment-resistant patients who had been ill for a long time were treated with clozapine or chlorpromazine. Patients taking clozapine had a much better response than patients taking chlorpromazine. Not only were the clozapine patients less psychotic, they were superior on all measurements—less depressed, less anxious, and scored better on the Brief Psychiatric Rating Scale (BPRS) anergia score than chlorpromazine patients. The data on efficacy of clozapine versus chlorpromazine in reducing blunted affect, motor retardation, and emotional withdrawal also suggested a broader spectrum of activity for clozapine, particularly in patients with negative symptoms. At the end of the 6-week study, the clozapine patients were still improving, while maximum response had been achieved in the chlorpromazine group: a longer treatment period in this study may have resulted in a more dramatic comparison between clozapine and chlorpromazine.

Dr. Marder considers the criteria for treatment resistance in the clozapine study of Kane et al. as too narrow. Some patients who improve dramatically on clozapine therapy are still floridly ill and may be ineligible for hospital discharge. More recent-onset patients who are less ill have the most to gain from a better antipsychotic if they are regarded as treatment refractory. Patients who have benefited the most from being switched to clozapine, risperidone, or olanzapine have been those who had persistent psychotic symptoms, but were falling short of success in college or on the job. The newer drugs make a dramatic difference in patients who are less ill, and allow them to reacquire self-confidence.

Dr. Marder reported the results of a recent double-blind, 29-week study[5] of clozapine and haloperidol. The 71 patients were refractory to treatment with conventional neuroleptics but still living in the community, ambulatory but with some hallucinations or delusions. Clozapine was vastly superior to haloperidol: at week 29, about 60% of the clozapine patients versus 12% of the haloperidol patients were rated as improved (≥ 20% reduction in BPRS psychosis factor scores). Despite the well-known side effects of clozapine (it is sedating, causes drooling and seizures, and causes agranulocytosis in 1%), many more of the haloperidol than clozapine patients dropped out; at week 29, nearly 80% of the patients receiving clozapine were still in the trial.

Trials with risperidone also suggest that it is efficacious and well tolerated in treatment-refractory patients, Dr. Marder reported. In a study by Ames et al.,[6] in which Dr. Marder was 1 of the investigators, patients rated as treatment refractory according to the strict criteria of Kane et al.,[4] were randomly assigned to receive 6 mg of risperidone or 15 mg of haloperidol daily. After the patient had been treated for 4 weeks with these fixed doses, the clinician was able to adjust the dose. There was greater overall improvement in patients receiving risperidone than haloperidol—more risperidone than haloperidol patients showed a 30%, 40%, or 50% improvement rate (reduction in Positive and Negative Syndrome Scale [PANSS] total scores), and there was a dramatic difference in how patients tolerated the 2 drugs. Antiparkinsonian drugs were required by 61% of the haloperidol patients, versus only 21% of the risperidone patients. Moreover, according to the Drug Attitude Inventory, patients were much more comfortable with risperidone than haloperidol.

Risperidone has also been shown to be as effective as clozapine in treatment-resistant patients, according to Dr. Marder. Bondolfi et al.[7] assigned 86 patients who were resistant to or intolerant of conventional neuroleptics to receive 6 mg/day of risperidone or 300 mg/day of clozapine for 8 weeks. Responses to treatment were similar in

the 2 groups: at treatment endpoint, 67% of the risperidone patients and 65% of the clozapine patients were improved (≥ 20% reduction in PANSS total scores). Risperidone, however, appeared to be better tolerated than clozapine in this study.

No studies have yet been published on the use of the newer atypical agents (olanzapine, quetiapine) in treatment-resistant patients. In studies of hospitalized patients with schizophrenia, these agents were effective, suggesting to Dr. Marder that they should be considered for treatment-refractory patients with negative symptoms.

Dr. Marder concluded with the following recommendations for treating patients with refractory illnesses. First, ascertain if the time on therapy has been sufficient to demonstrate results. Many patients are not going to respond to an antipsychotic in 2 or 3 weeks, and, with clozapine or risperidone, Dr. Marder would consider a minimum trial to be about 3 months. The second issue is drug bioavailability: Is the drug getting to the brain? There are many reasons why a drug will fail to be absorbed (including rapid drug metabolism and drug interactions), but the most common reason a drug fails to get into the brain is because the patient fails to take it.

If a patient is doing poorly, it is time to aggressively look for a better antipsychotic. Clozapine is not a first choice because it is a difficult drug to administer. Starting with risperidone (or perhaps olanzapine) before clozapine would be appropriate. In the past, clinicians would switch from 1 conventional neuroleptic to another, but the literature suggests that there is cross-resistance in conventional drugs, and a newer antipsychotic would be more useful in these refractory cases.

Increasing the dose of conventional neuroleptics above the usual range is rarely effective. Thus patients who fail to do well in high-dose trials of conventional drugs deserve a trial on a newer antipsychotic. Supplementation of the antipsychotic with other agents, such as lithium, benzodiazepines, carbamazepine, or high-dose propranolol, has been ineffective.

When risperidone first became available, many patients who were switched from clozapine to risperidone experienced severe psychotic relapses. Dr. Marder concludes that in many cases this resulted from switching too quickly. Today, it is suggested that patients be switched from clozapine to risperidone using a prolonged cross-titration. In Dr. Marder's practice, changing a patient's treatment from clozapine to risperidone or olanzapine never takes less than a month.

Responding to a question about combining risperidone with clozapine, Dr. Marder stated that he recommends that it is always better to try each drug as monotherapy before combining them. However, he has noted that, while a patient is receiving both drugs during a switch from clozapine to risperidone, sometimes the patient suddenly improves and is vastly happier than he or she has been in years. This has not been documented in careful studies, however.

References

1. National Institute of Mental Health and Psychopharmacology Service Center Collaborative Study Group. Phenothiazine treatment in acute schizophrenia. Arch Gen Psychiatry 1964;10:246–261
2. Janicak PG, Davis JM, Preskorn SH, et al. Principles and Practice of Psychopharmacology. Baltimore, Md: Williams & Wilkins; 1993:93–184
3. van Putten T, Marder SR, Wirshing WC, et al. Neuroleptic plasma levels. Schizophr Bull 1991;17:197–216
4. Kane J, Honigfeld G, Singer J, et al and the Clozaril Collaborative Study Group. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988:45:789–796
5. Schooler NR, Kane JM, Marder SR, et al. Efficacy of clozapine vs haloperidol in a long term clinical trial: preliminary findings [abstract]. Schizophr Res 1995;15:165
6. Ames D, Wirshing WC, Barringer D, et al. Treatment-resistant schizophrenia: efficacy of risperidone versus haloperidol. In: New Research Program and Abstracts of the 150th Annual Meeting of the American Psychiatric Association; May 20, 1997; San Diego, Calif. Abstract NR214:126
7. Bondolfi G, Dufour H, Patris M, et al. Risperidone versus clozapine in treatment-resistant chronic schizophrenia: a randomized double-blind study. Am J Psychiatry 1998;155:499–504

Pharmacotherapy of Late-Life Psychoses

Dr. Dilip V. Jeste described the costs, adverse effects, and special problems of treating geriatric psychoses with both conventional neuroleptics and newer atypical antipsychotics. Newer antipsychotics are more expensive, but may be more cost effective in geriatric patients, Dr. Jeste concluded. They result in greater improvement in both positive and negative symptoms of psychosis, reduce the rate of hospitalization, and have fewer adverse effects than conventional neuroleptics. Newer antipsychotics may also improve compliance and result in a better quality of life for geriatric patients, but more studies are needed in this population. Special precautions for clinicians prescribing newer antipsychotics with late-life patients include using lower doses, monitoring side effects, avoiding nonessential medications, and discontinuing treatment as soon as appropriate.

According to Dr. Jeste, "late-life psychosis" is a broad differential diagnosis encompassing the prototypical chronic psychosis, schizophrenia, and other diseases with psychotic symptoms (dementia, major depression, bipolar illness, etc.). Geriatric psychoses may also include delusional disorder and psychoses secondary to other medical conditions (brain tumor, stroke, and metabolic encephalopathies). Psychosis secondary to levo-

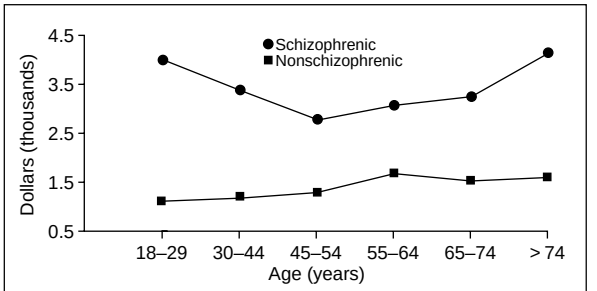
dopa treatment for Parkinson's disease is an additional type of psychosis seen primarily in geriatric patients.

A recent study[1] conducted by Dr. Jeste and colleagues in the San Diego County Public Mental Health system showed that schizophrenia represents a significant per-patient expense in both younger and older patients (Figure 1). Important reasons for the high mental health care costs in the elderly may include cognitive impairment and adverse effects of medication. Dr. Jeste reported that cognitive impairment is an integral feature of schizophrenia—to the extent that schizophrenia can be considered primarily a neurocognitive disease. Studies show the severity of cognitive impairment in schizophrenia determines not only treatment costs and disease outcome, but also the extent of a patient's ability to function in day-to-day activities.

Conventional neuroleptics have variable effects on cognition in the elderly. Higher doses and longer treatment periods may cause a decrease in performance on some cognition tasks, according to Dr. Jeste. Patients who are more severely impaired at baseline may have worse responses to treatment. Low-potency neuroleptics, such as thioridazine, are highly anticholinergic and may impair cognitive abilities. A study of patients with Alzheimer's disease by Devanand et al.[2] demonstrated that high-dose haloperidol caused a significant worsening of Mini-Mental State Examination (MMSE) scores. At low doses, however, conventional neuroleptics can improve some cognitive aspects (attention and learning) in schizophrenic patients. At higher doses or if accompanied by anticholinergics, they are likely to decrease certain cognitive abilities, particularly in the elderly.

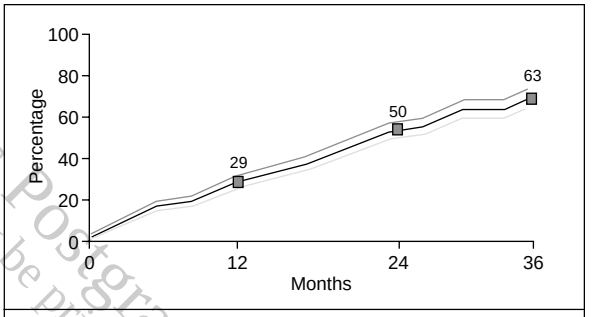
Tardive dyskinesia (TD) is a potentially disabling adverse effect of treatment with conventional neuroleptics: 4% to 5% of younger adults treated with conventional neuroleptics develop TD per year, but the incidence is much higher in elderly patients. In a large study[3] of a relatively stable, heterogeneous group of older outpatients on low doses of conventional neuroleptics (e.g., 2 to 2.5 mg/day of haloperidol), the incidence of TD was nearly 6 times the rate for younger adults (Figure 2). The most important risk factor for TD in this population was the cumulative amount of neuroleptics: the greater the dose and the longer the duration of treatment, the higher the risk. The findings also suggested that drugs likely to produce extrapyramidal symptoms may have a higher risk of producing TD.

Figure 1. Mean Per-Patient Costs of Treating Schizophrenic and Nonschizophrenic Patients in the San Diego County Mental Health System, by Age*



*Reprinted with permission from Cuffel et al.[1]

Figure 2. Cumulative Incidence of Neuroleptic-Induced Tardive Dyskinesia in 439 Middle-Aged and Elderly Patients Treated With a Conventional Neuroleptic*



*Reprinted with permission from Jeste et al.[3]

The main indications for clozapine in the elderly are treatment-resistant schizophrenia, severe TD, and Parkinson's disease with psychotic symptoms, Dr. Jeste advised. Clozapine's effects on cognitive function in elderly patients have been inconclusive.

The most serious adverse effect associated with clozapine is agranulocytosis, which occurs in about 1% of patients; seizures occur in about 5%. Anticholinergic toxicity of clozapine, experienced as mouth dryness, constipation, urinary retention, and confusion, can be more of a problem in the elderly than in younger patients. The doses of clozapine for the elderly should be considerably lower than for younger adults, Dr. Jeste warned. The recommended starting dose should be as low as 6.25 to 12.5 mg/day, and maintenance doses exceeding 100 mg/day should be avoided. Some patients need and can tolerate only 50 mg/day, and there is no reason to exceed that dose in these patients, according to Dr. Jeste.

Dr. Jeste reported that risperidone has shown promise in elderly patients. For example, in a 12-week study[4] of 103 elderly patients with schizophrenia (in 75%) or schizoaffective disorders (in 25%), risperidone significantly reduced the severity of psychopathology (total and subscale PANSS scores) and was well tolerated.

Elderly demented patients have also responded to risperidone. In a recent double-blind, placebo-controlled

study,[5] 625 patients (73% with Alzheimer's disease, 15% with vascular dementia, and 12% with mixed dementia) were randomly assigned to receive 0.5 mg, 1 mg, or 2 mg of risperidone daily or matching placebo for 12 weeks.

Dr. Jeste, who was one of the investigators in this study, reported that on both of the key measures of efficacy, the BEHAVE-AD scale and the Cohen-Mansfield Agitation Inventory, patients receiving 1 or 2 mg/day of risperidone showed significant improvement: reductions in psychosis and in the severity and frequency of aggressive behavior were significantly greater than in patients receiving placebo. The incidence of adverse events was similar in patients receiving placebo or 1 mg/day of risperidone, but higher in patients receiving 2 mg/day of risperidone than placebo, so that the recommended risperidone dose in elderly demented patients is 1 mg/day, according to Dr. Jeste.

The effects of risperidone on cognition in elderly patients have been investigated in 3 small trials, Dr. Jeste reported,[6] and in each significant improvements were shown by the patients (MMSE scores).

Risperidone, however, is not without side effects, Dr. Jeste cautioned. The 2 side effects of risperidone that are of particular concern in the elderly are postural hypotension and extrapyramidal symptoms—the higher the dose, the greater the risk for developing parkinsonism or other symptoms. Somnolence is also seen at higher doses. It is important to follow recommendations and use the lowest effective dose in the elderly. In older patients who have a diagnosis of dementia or Parkinson's disease or have hypotension, the dose should not exceed 1 mg/day. Patients with schizophrenia or other psychotic disorders with no complications may be able to tolerate doses up to 2.5 mg/day.

In summary, Dr. Jeste pointed out that the atypical agents are more effective than conventional agents for positive and negative symptoms in the elderly, have fewer side effects, and reduce hospitalization rates. They probably increase compliance and lead to a better quality of life. He stressed that psychosocial management is also critical in treating schizophrenia, particularly since antipsychotics do not cure this or any other psychotic disorder.

Responding to a questioner, Dr. Jeste said that patients in the controlled double-blind study who were assessed by the BEHAVE-AD scale exhibited clinical as well as rating-scale improvement on risperidone therapy. Responding to another question about risperidone, Dr. Jeste pointed out that experience suggests that patients with Parkinson's disease should receive 1 mg/day or less since higher doses reportedly increased the severity of parkinsonian symptoms.

REFERENCES

1. Cuffel BJ, Jeste DV, Halpain M, et al. Treatment costs of community mental health services for schizophrenia by age cohorts. Am J Psychiatry 1996;153: 870–876
2. Devanand DP, Sackeim HA, Brown RP, et al. A pilot study of haloperidol treatment of psychosis and behavioral disturbance in Alzheimer's disease. Arch Neurol 1989; 46:854–857
3. Jeste DV, Rockwell E, Harris MJ, et al. Conventional versus newer antipsychotics. Am J Geriatr Psychiatry. In press
4. Madhusoodanan S, Brecher M, Brenner R, et al. Efficacy and tolerability of risperidone in elderly patients with psychotic disorders. Poster presented at the American Association for Geriatric Psychiatry 10th Annual Meeting; March 2–5, 1997; Lake Buena Vista, Fla
5. Katz I, Jeste DV, Mintzer JE, et al. Risperidone in the treatment of psychosis and behavioral disturbances in patients with dementia: a placebo-controlled, randomized, double-blind trial in 625 patients. Poster presented at the 36th annual meeting of the American College of Neuropsychopharmacology; December 8–12, 1997; Kamuela, Hawaii
6. Jeste DV, Eastham JH, Lacro JP, et al. Management of late-life psychosis. J Clin Psychiatry 1996;57(suppl 3):39–45

Treating the Persistently Violent Patient

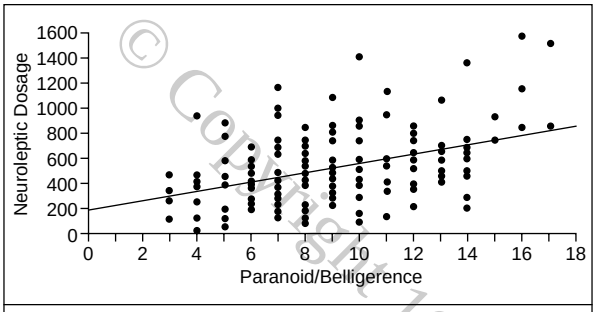
In recent years, the number of violent patients in psychiatric facilities has increased, and clinicians' interest in treating these patients has increased accordingly. Five percent of inpatients are responsible for 50% of the violent incidents in psychiatric hospitals, Dr. Jan Volavka reported. Current therapies for persistent violent behavior include typical and atypical antipsychotics, mood stabilizers, antidepressants, anxiolytics, and β-adrenergic blockers. Results with atypical antipsychotics, mood stabilizers, and serotonin selective reuptake inhibitors (SSRIs) are promising in persistently violent patients. Results with conventional neuroleptics and benzodiazepines are less encouraging.

Aggression is a discrete event, Dr. Volavka noted. Research in aggression is similar to epilepsy research—a patient is either currently engaged in violence or he/she is not. A patient is considered "violent" if he/she exhibits overt physical aggression against others or objects or needs therapeutic seclusion or restraint.

Many psychiatrists respond to increasing violence in patients by increasing doses of antipsychotics (Figure 1).[1] However, high doses of antipsychotics may be counterproductive. For example, they can cause akathisia, which can actually increase violent behavior according to 2 mechanisms: first, the inner restlessness experienced by patients with akathisia makes them irritable, and, second, patients with akathisia move fast, and by moving fast in circumscribed spaces, they often invade another's personal space. In Dr. Volavka's opinion, these high doses may reflect the psychiatrist's fear of the patient rather than rational pharmacology.

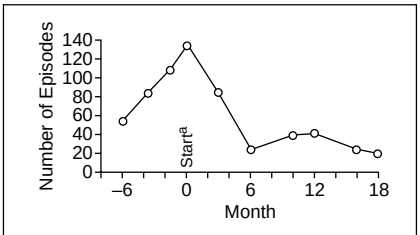
Dr. Volavka reported that clozapine has been shown to be effective in the

Figure 1. Relationship Between Scores on the PANSS Paranoid/Belligerence Cluster and Neuroleptic Dose (mg of chlorpromazine equivalents) in 155 Newly Admitted Schizophrenic Patients*



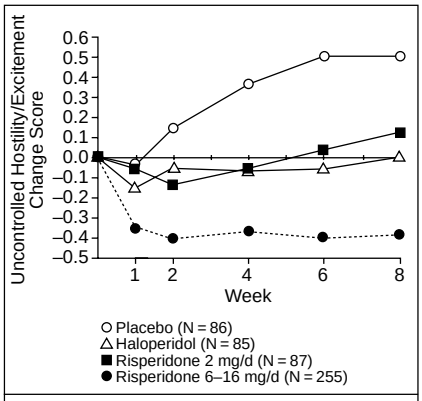
*Reprinted with permission from Troisi et al.[1] Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 2. Number of Violent Episodes Among 100 Inpatients of a State Hospital Before and After Clozapine Treatment*



*Reprinted with permission from Wilson and Claussen.[2]
[a]Clozapine treatment began in month 0.

Figure 3. Change Scores on the Uncontrolled Hostility/Excitement Factor (PANSS-derived) in Patients Receiving Placebo, Haloperidol, or Risperidone*



*Reprinted with permission from Marder et al.[7]

treatment of some violent patients. For example, in a study of 100 patients with chronic psychotic disorders in a state psychiatric hospital, Wilson and Claussen[2] reported a dramatic decrease in the number of violent episodes after the introduction of clozapine (Figure 2). Dr. Volavka and colleagues conducted a retrospective study[3] of 331 treatment-resistant patients with chronic schizophrenia who were treated with clozapine for 12 weeks. At baseline, 31.4% of the patients showed a high level of hostility on the Brief Psychiatric Rating Scale; this was reduced to 6.7% after 6 weeks' treatment with clozapine and to 3.1% at 12 weeks. Dr. Volavka noted that these effects of clozapine were particularly striking in patients who showed the highest pretreatment levels of hostility, suggesting that clozapine has antiaggressive effects in patients who need it most.

Encouraged by the clozapine results, Dr. Volavka investigated whether risperidone was also antiaggressive. Using data from the North American trial of risperidone in chronic schizophrenia,[4,5] Dr. Volavka and colleagues[6] identified 139 patients with high scores on the hostility item of the PANSS. Risperidone had a greater selective effect on hostility in these patients than did haloperidol or placebo.

These findings were confirmed in a recent factor analysis[7] of the PANSS data from the North American trial. Factor analysis identified 5 dimensions or factors of schizophrenia, 1 of which was labeled "uncontrolled hostility/excitement." Risperidone was significantly more effective than haloperidol in reducing the scores on this factor (Figure 3).

Turning to mood stabilizers, Dr. Volavka noted they are frequently used to control aggression and there is some evidence for their effectiveness. In placebo-controlled studies, carbamazepine has been shown to reduce aggressive behavior in patients with a broad spectrum of diagnoses.[8,9] Lithium has been used to reduce aggressive behavior in children with conduct disorder[10] and in nonpsychotic prisoners.[11]

Serotonin selective reuptake inhibitors are just beginning to be investigated in aggressive patients, and Dr. Volavka noted that, in theory, increased serotonergic activity is desirable since an established principle is that aggression is associated with low serotonergic activity. Indeed, trials of fluoxetine[12] and citalopram[13] suggest that they have antiaggressive effects.

Anxiolytics and β-blockers may be effective in the management of aggression, but some evidence suggests that adjunctive clonazepam may worsen the problem. Case reports indicate that β-blockers may reduce aggression associated with head injuries, seizures, mental retardation, dementia, conduct disorder, or, perhaps, attention-deficit/hyperactivity disorder, as well as other disorders.

Nadolol has been shown to reduce overt aggression in schizophrenic patients[14] and may act through peripheral components of akathisia or anxiety, according to Dr. Volavka. Beneficial effects of β-blockers may not occur for the initial 4 to 6 weeks of treatment. Dose-limiting side effects include hypotension and bradycardia.

Responding to a questioner, Dr. Volavka noted that intermittent explosive behavior associated with borderline disorder may respond to anticonvulsants, particularly since explosive behavior is also linked to temporal epilepsy. Carbamazepine

may be effective, he suggested, even in patients with normal electroencephalograms.

Should benzodiazepines be given with atypical antipsychotics to newly admitted, agitated patients with psychosis? Dr. Volavka said he opposed coadministration of benzodiazepines during the first 4 to 5 weeks of clozapine treatment, since an adverse interaction between these agents reportedly caused several deaths. Apparently, the danger is maximal in initial stages of clozapine-dose titration. The combination appears to be safer in later stages of clozapine treatment, Dr. Volavka added.

REFERENCES

1. Troisi A, Pasini A, De Angelis F, et al. Paranoid/belligerence and neuroleptic dosage in newly admitted schizophrenic patients. J Clin Psychopharmacol 1997;17:84–87
2. Wilson WH, Claussen AM. 18-Month outcome of clozapine treatment for 100 patients in a state psychiatric hospital. Psychiatr Serv 1995;46:386–389
3. Volavka J, Zito JM, Vitrai J, et al. Clozapine effects on hostility and aggression in schizophrenia. J Clin Psychopharmacol 1993;13:287–289
4. Chouinard G, Jones B, Remington B, et al. A Canadian multicenter, placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of schizophrenic patients. J Clin Psychopharmacol 1993;13:25–39
5. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825–834
6. Czobor P, Volavka J, Meibach RC. Effect of risperidone on hostility in schizophrenia. J Clin Psychopharmacol 1995;15:243–249
7. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997;58:538–546
8. Okuma T, Yamashita I, Takahashi R, et al. A double-blind study of adjunctive carbamazepine versus placebo on excited states of schizophrenia and schizoaffective disorders. Acta Psychiatr Scand 1989;80:250–259
9. Cowdry RW, Gardner DL. Pharmacotherapy of borderline personality disorder: alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. Arch Gen Psychiatry 1988;45:111–119
10. Campbell M, Adams PB, Small AM, et al. Lithium in hospitalized aggressive children with conduct disorder: a double-blind and placebo-controlled study. J Am Acad Child Adolesc Psychiatry 1995;34:445–453. Erratum 1995;34:694
11. Sheard MH, Marini JL, Bridges CI, et al. The effect of lithium on impulsive aggressive behavior in man. Am J Psychiatry 1976;133:1409–1413
12. Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. Arch Gen Psychiatry 1997;54:1081–1088
13. Vartiainen H, Tiihonen J, Putkonen A, et al. Citalopram, a selective serotonin reuptake inhibitor, in the treatment of aggression in schizophrenia. Acta Psychiatr Scand 1995;91:348–351
14. Ratey JJ, Sorgi P, O'Driscoll GA, et al. Nadolol to treat aggression and psychiatric symptomatology in chronic psychiatric inpatients: a double-blind, placebo-controlled study. J Clin Psychiatry 1992;53:41–46

SYMPOSIA AND PRESENTERS

These highlights are derived from 3 symposia held at the 150th Annual Meeting of the American Psychiatric Association, San Diego, California, May 17–22, 1997, and sponsored by Janssen Research Foundation, Titusville, New Jersey. The chair of the first symposium, "Antipsychotics in Unique Patient Populations," was Stephen R. Marder, M.D., Professor and Vice Chair, Department of Psychiatry, UCLA School of Medicine, Los Angeles, California. The participants were Jan Volavka, M.D., Ph.D., Professor of Psychiatry, New York University, New York, New York; Daniel J. Luchins, M.D., Associate Professor of Psychiatry, The University of Chicago, Chicago, Illinois; Paul E. Keck, Jr., M.D., Associate Professor of Psychiatry and Pharmacology, University of Cincinnati College of Medicine, Cincinnati, Ohio; and Gabrielle A. Carlson, M.D., Professor of Psychiatry and Pediatrics, SUNY at Stony Brook, Stony Brook, New York. The chair of the second symposium, "Psychiatric Management of Long-Term Care Patients," was Dilip V. Jeste, M.D., Director, Geriatric Psychiatry Clinical Research Center, University of California, San Diego, and V.A. Medical Center, San Diego, California. The participants were Peter J. Whitehouse, M.D., Ph.D., Director, Alzheimer Center, University Hospitals of Cleveland, Cleveland, Ohio; Ira R. Katz, M.D., Ph.D., Director, Section of Geriatric Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania; George S. Alexopoulos, M.D., Director, Specialized Services Division, The New York Hospital—Cornell Medical Center, White Plains, New York; Maurice W. Dysken, M.D., Director, GRECC Program, Minneapolis VA Medical Center, Minneapolis, Minnesota; and Soo Borson, M.D., Director of Geriatric Psychiatry, University Medical Center, University of Washington, Seattle, Washington. The chair of the third symposium, "Challenge: Making the Most of Therapy With Atypical Antipsychotics," was Joseph P. McEvoy, M.D., Associate Professor, Department of Psychiatry, Duke University, Durham, North Carolina. The participants were William C. Wirshing, M.D., Professor of Clinical Psychiatry, UCLA School of Medicine, Los Angeles, California; Del D. Miller, Pharm.D., M.D., Assistant Professor of Psychiatry, University of Iowa College of Medicine, Department of Psychiatry, Iowa City, Iowa; Prakash S. Masand, M.D., Professor of Psychiatry, SUNY Health Science Center, Department of Psychiatry, Syracuse, New York; and Richard J. Wyatt, M.D., Chief, Neuropsychiatry Branch, National Institute of Mental Health, Washington, District of Columbia. ❑

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