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

Part I: Unique Patient Populations

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 tested 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-
Fluphenazine Levels

Side Effects as a Function of Plasma

Figure 2. Improvement and Disabling

patients who had been ill for a long
time were treated with clozapine or
chlorpromazine. Patients taking cloza-
pine 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)
aneurgia score than chlorpromazine pa-
tients. The data on efficacy of cloza-
pine versus chlorpromazine in reduc-
ing blunted affect, motor retardation,
and emotional withdrawal also sug-
ggested a broader spectrum of activity
for clozapine, particularly in patients
with negative symptoms. At the end of
the 6-week study, the clozapine pa-
tients were still improving, while max-
imum response had been achieved in
the chlorpromazine group: a longer
treatment period in this study may have
resulted in a more dramatic compari-
son between clozapine and chlorpro-
mazine.

Dr. Marder considers the criteria for
treatment resistance in the clozapine
study of Kane et al. too narrow. Some
patients who improve dramati-
cally on clozapine therapy are still flor-
idly ill and may be ineligible for hospi-
tal discharge. More recent-onset
patients who are less ill have the most
to gain from a better antipsychotic if
they are regarded as treatment refrac-
tory. Patients who have benefited the
most from being switched to cloza-
pine, risperidone, or olanzapine have
been those who had persistent psych-
otic 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-confi-
dence.

Dr. Marder reported the results of a
recent double-blind, 29-week study of
clozapine and haloperidol. The 71 pa-
tients were refractory to treatment with
conventional neuroleptics but still liv-
ing in the community, ambulatory but
with some hallucinations or delusions.

Clozapine was vastly superior to hal-
operidol: at week 29, about 60% of the
clozapine patients versus 12% of the
haloperidol patients were rated as im-
proved (≥20% reduction in BPRS psy-
chosis 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., in which Dr. Marder was 1 of the
investigators, patients rated as treat-
ment refractory according to the strict
criteria of Kane et al., 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 haloperi-
dol—more risperidone than haloperi-
dol 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 tol-
erated 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 Inven-
tory, patients were much more com-
fortable with risperidone than haloperi-
dol.

Risperidone has also been shown to
be as effective as clozapine in treat-
ment-resistant patients, according to
Dr. Marder. Bondolfi et al. 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

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

<table>
<thead>
<tr>
<th>Percentage of Patients</th>
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<tbody>
<tr>
<td>Worse</td>
</tr>
<tr>
<td>No Change</td>
</tr>
<tr>
<td>Minimally Improved</td>
</tr>
<tr>
<td>Much Improved</td>
</tr>
</tbody>
</table>

*Reprinted with permission from van Putten et al.*

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

*Data from National Institute of Mental Health and Janicak et al.*

*Reprinted with permission from van Putten et al.*

stantially improved, but close to the
same proportion of patients experi-
enced side effects so serious that any
reasonable clinician would have low-
ered the dose or changed treatment.

Dr. Marder proposed that treatment
resistance did not really become a re-
search issue until publication of the
clozapine multicenter study by Kane
et al. in 1988. In this study, a group of
floridly psychotic, treatment-resistant
patients who had been ill for a long
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

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.

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.\(^4\)

Dr. Jeste reported that risperidone has shown promise in elderly patients. For example, in a 12-week study\(^5\) 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

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\(^1\) Reprinted with permission from Jeste et al.\(^3\)

\(^2\) Reprinted with permission from Cuffel et al.\(^1\)

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

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Schizophrenic</th>
<th>Nonschizophrenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–29</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>30–44</td>
<td>2.5</td>
<td>2.0</td>
</tr>
<tr>
<td>45–54</td>
<td>3.5</td>
<td>3.0</td>
</tr>
<tr>
<td>55–64</td>
<td>4.5</td>
<td>4.0</td>
</tr>
</tbody>
</table>

*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***

<table>
<thead>
<tr>
<th>Months</th>
<th>Percentage</th>
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<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
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<tr>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>36</td>
<td>30</td>
</tr>
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*Reprinted with permission from Jeste et al.\(^4\)*
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**


**Academic Highlights**

**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). 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...
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 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 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, Dr. Volavka and colleagues 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 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 that 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. Lithium has been used to reduce aggressive behavior in children with conduct disorder and in nonpsychotic prisoners.

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 and citalopram 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 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

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**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. 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. 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.
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


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, 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, Special 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, “Challenges: 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. McEvoy, 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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