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

Part II: Special Considerations

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 first part of this series, which highlighted unique patient populations, appeared in the May 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.

Atypical Agents in Nonschizophrenic Disorders

Indications for atypical antipsychotics other than schizophrenia so far have included bipolar disorder, major depression, schizoaffective disorder, dementia, delirium, obsessive-compulsive disorder, Tourette's syndrome, and mental retardation, Dr. Prakash S. Masand reported.[1] In 1997, only 38% of risperidone prescriptions in the United States were for the treatment of schizophrenia, while 20% were for bipolar disorder, 11% for dementia, and the rest (31%) for the other disorders listed above.[2]

In reference to bipolar patients, Dr. Masand first noted that 20% to 50% of acutely manic patients have psychotic symptoms and 58% of bipolar patients have a lifetime history of psychosis; 18% of bipolar patients have Schneiderian first-rank symptoms of schizophrenia, including thought broadcasting, thought insertion or withdrawal, or thoughts spoken aloud.[3,4] Dr. Masand therefore advised clinicians to rule out a mood disorder before diagnosing schizophrenia in patients with these symptoms.

Bipolar patients today are typically treated initially with a mood stabilizer such as lithium, valproic acid, or carbamazepine. Unresponsive patients may receive combinations of different mood stabilizers, and benzodiazepines may be added. Many patients in the past received adjunctive conventional neuroleptics; however, only 35% to 60% of patients responded to these, while long-term neuroleptic therapy frequently caused tardive dyskinesia and had less benefit than maintenance lithium or carbamazepine, and sometimes exacerbated depression.

Dr. Masand noted, however, that whether psychotic symptoms are present or not, data show that many patients do not enjoy long-term stability with mood stabilizers alone and need maintenance adjunctive antipsychotic therapy.[5] Currently, atypical agents are the drugs of choice for acute or maintenance therapy in these patients, Dr. Masand stated.

Risperidone in particular has been shown to have mood-stabilizing properties predominantly because of its potent 5-HT_2 antagonism as well as α_2-adrenoceptor blockade.[6] Open studies have shown that treatment-refractory bipolar disorder often responds to risperidone alone or as an adjunct to conventional mood stabilizers.[7]

Some 65% to 85% of all bipolar subtypes respond to 2–3 mg/day of risperidone, Dr. Masand indicated.[8] A potential drawback is that mania or hypomania has occurred in a few patients not on mood stabilizers when treated with risperidone and other atypical agents.[9] However, it appears that the atypical agents did not cause most of the lapses into mania or hypomania; instead, they were due to recent discontinuation of the previous neuroleptic or mood stabilizer or to spontaneous cycling.[10]

Clozapine has been shown to be effective as monotherapy or when com-

bined with mood stabilizers in 50% to 90% of bipolar patients, according to Dr. Masand.[11] Manic subtypes appeared to respond better to clozapine combined with mood stabilizers than depressed or mixed subtypes. Clozapine was also efficacious in treatment-refractory bipolar patients.[12] In schizoaffective bipolar patients either in the manic or mixed state, olanzapine was as effective as haloperidol on several measures including conceptual disorganization, hostility, and excitement.[13] Schizoaffective patients in depressed stage worsened with haloperidol but improved with olanzapine, indicating that the atypical agents can actually improve mood symptoms in bipolar patients.

In the treatment of elderly patients with psychosis or dementia, Dr. Masand observed that low doses of clozapine or risperidone are efficacious and cause fewer extrapyramidal symptoms (EPS) and less orthostatic hypotension, confusion, and delirium than the conventional neuroleptics that were long used in this population.[14–17] One of the important advantages of the atypicals in elderly patients is their low propensity to cause tardive dyskinesia, whose frequency is several times higher in elderly than younger patients, as noted by Dr. Jeste in his presentation on the pharmacotherapy of late-life psychoses (see the May ACADEMIC HIGHLIGHTS[18]).

Dr. Masand cited data from a recent double-blind study[19] of 625 patients with severe dementia in whom risperidone at 1 mg/day and 2 mg/day significantly reduced psychotic symptoms and the frequency and severity of aggressiveness. Dr. Jeste reports the findings of this study in more detail (see the May ACADEMIC HIGHLIGHTS[18]). In contrast, olanzapine (at doses of 1–8 mg/day) was found to be no more efficacious than placebo in treating psychotic and behavioral manifestations of Alzheimer's dementia in 238 elderly patients.[20]

No efficacy studies of quetiapine or sertindole in elderly patients have yet been published, but studies of the tolerability of these 2 new atypicals in elderly patients have been presented at psychiatric meetings. Sertindole was well tolerated in 20 patients with dementia treated for 16 days.[21] In a long-term study[22] of quetiapine in 15 patients with idiopathic or organic psychosis, 12 completed 16 weeks of treatment and 6 completed a year of treatment; the frequency of side effects, however, was quite high (agitation reported by 53%, somnolence by 40%, and constipation and asthenia each by 27%).

Haloperidol has been the gold standard in the treatment of delirium, according to Dr. Masand. However, in a study of risperidone by Dr. Masand and his colleague,[23] 11 patients with delirium (mean age = 51 years) received 1 to 3 mg/day of risperidone for about 9 days, and 73% of the patients improved. Risperidone at these low doses was also well tolerated.

Turning to obsessive-compulsive disorder, Dr. Masand observed that many patients with this disorder respond to risperidone adjunctive to antidepressants. In 3 open-label trials,[24–26] approximately 60% to 70% of the patients responded to 2 to 3 mg/day of adjunctive risperidone. Atypical agents may exacerbate obsessive-compulsive symptoms in patients with comorbid schizophrenia, Dr. Masand warned.

Behavioral symptoms in pervasive developmental disorder often respond to risperidone, Dr. Masand reported; moreover, risperidone is better tolerated and chronic treatment poses less risk of tardive dyskinesia compared with the conventional neuroleptics traditionally given to this population.

In the double-blind placebo-controlled crossover study of Vanden Borre et al.,[27] 37 mentally retarded patients with persistent behavioral problems received adjunctive risperidone (4–12 mg/day) for 3 weeks; this was followed by a 1-week single-blind washout period and another 3 weeks of double-blind crossover medication. In the second 3-week study period, patients receiving risperidone showed significant reductions in scores on the Aberrant Behavior Checklist (ABC), compared with no effect in the placebo group. Risperidone frequently caused drowsiness, but no significant exacerbation of existing EPS.

Dr. Masand also cited several open studies. McDougle et al.[28] found that optimal risperidone doses of approximately 2 mg/day for 12 weeks improved measures of aggression and impulsivity in 18 youngsters (mean ± SD age = 10.2 ± 3.7 years) with pervasive developmental disorder. Among 28 mentally retarded patients (aged 19–57 years) with aggressive behavior refractory to conventional neuroleptics, DeLeon et al.[29] reported that 18 were improved on the ABC scale after 12 weeks of treatment with 1 to 2 mg/day of add-on risperidone.

Horrigan and Barnhill[30] reported that risperidone (modal dose = 0.5 mg/day) caused prompt significant improvement in 11 outpatients (mean age = 18.3 years) with explosivity and aggression associated with autism and mental retardation. Patients were assessed by means of clinical interviews and caregivers' completion of the Conners Parent-Teacher Questionnaire. No patient had EPS.

Finally, Dr. Masand warned of potential, clinically significant drug interactions with atypical agents in patients receiving medications for concurrent medical or psychiatric conditions. The isoenzymes that metabolize these agents are the same as those for a number of other, commonly used medications. For example, since paroxetine and fluoxetine can increase risperidone blood levels, risperidone doses may need to be decreased to avoid side effects. Cigarette smoking, carbamazepine, and phenytoin decrease clozapine and olanzapine blood levels; and sertindole levels may be

increased by paroxetine, fluoxetine, fluvoxamine, cimetidine, ketoconazole, and erythromycin.

Responding to a questioner, Dr. Masand stated that chronic cigarette smoking may cause a 30% to 40% reduction in clozapine or olanzapine blood levels. Drug doses should be adjusted accordingly.

Replying to another questioner, Dr. Masand suggested it was reasonable to combine atypical and conventional agents in treatment-resistant patients. Often the best combination is a low dose of the conventional agent and an adequate dose of the atypical agent. The optimum doses of the combination may be determined when the patient reports significant improvement at some point during the switch from a conventional to an atypical agent while the patient is still receiving both agents.

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Side Effects of Atypical Antipsychotics

Dr. William C. Wirshing suggested that atypical antipsychotics are pharmacologically diverse but share this key defining feature: their dose-response characteristics exhibit a range of antipsychotic activity that is more or less separate from the range of extrapyramidal neurotoxicity, whereas traditional neuroleptics have little or no separation.[1] Thus, therapeutic doses of atypical agents are associated with lower incidences of acute EPS compared with their conventional counterparts.[2,3]

Dr. Wirshing reviewed the incidence of non-EPS side effects associated with the atypical agents. The most important of these include arrhythmogenic potential, sinus and reflex tachycardia, orthostatic hypotension, prolactin elevation, and weight gain.[4–7] These are largely due to their α-adrenergic,

muscarinic M_1, histaminic H_1, and 5-HT_{2C} receptor antagonism. Some sexual side effects are due to histaminic H_1 and serotonin 5-HT_2 receptor antagonism, and weight gain may be related to H_1 and 5-HT_{2C} blockade.

Overall, the newer agents require clinicians to be more alert for certain toxicities they may not be accustomed to seeing, Dr. Wirshing cautioned. For example, the elderly may be intolerant to antimuscarinic and anti-α-adrenergic action; and weight gain can be problematic or not, depending on the patients.[8–12]

Although atypical agents have clinically significant toxicities related to their α-adrenergic and muscarinic affinities, Dr. Wirshing noted that these agents do not necessarily follow the simple rule taught in medical school: high-potency drugs such as haloperidol weakly antagonize α-adrenergic and muscarinic receptors, whereas low-potency agents such as chlorpromazine potently antagonize these receptors.

The potentially fatal ventricular arrhythmia torsades de pointes is associated with all conventional neuroleptics and also seems to be an appreciable threat with sertindole, whose release in the United States has been postponed. These agents may prolong the QT interval, the vulnerable depolarization and repolarization period in which torsades may be triggered by normal ventricular premature contractions and may lead to sudden cardiac death.[13,14]

The risk of sudden cardiac death with atypical and standard agents is unpredictable as far as we know, Dr. Wirshing stated. The same unpredictability is seen with the type 1 antiarrhythmics such as quinidine; in most hearts, quinidine is antiarrhythmic, but in some it is proarrhythmic. With antipsychotic agents, however, the risk is extremely small and probably less than with tricyclic antidepressants. Even the most arrhythmogenic antipsychotic agent, thioridazine, poses less risk than the tricyclics.

Far more common side effects with atypical agents are sinus and reflex tachycardia and postural hypotension. Sinus tachycardia is caused by a direct antimuscarinic vagolytic effect on the myocardium. Reflex tachycardia is a compensatory reaction to decreased peripheral-vascular resistance caused by α_1-adrenoceptor blockade. Postural hypotension is a by-product of α_1-adrenoceptor blockade.

Risperidone has no appreciable antimuscarinic activity[15]; thus, a tachycardia caused by risperidone is a reflex tachycardia. Dr. Wirshing advised treating the tachycardia with an α_1-adrenoceptor agonist, which will eliminate the reflex by increasing peripheral vascular resistance.

Sexual toxicities may be more significant with atypical agents than conventional agents, according to Dr. Wirshing. Some may be due to prolactin elevation as a result of D_2 blockade in the hypothalamus, while others are secondary to α_1-adrenergic activity, possibly H_1 blockade, and, probably, 5-HT_2 blockade. They may include retrograde ejaculation, failure of ejaculation, delayed orgasm, and reduced libido.[16]

Treatment options include reduced doses, though Dr. Wirshing noted that this does not always succeed. The α-agonist ephedrine may resolve ejaculatory disorders in, perhaps, 30% of patients. Approximately 20% adjust to the problem or the problem spontaneously resolves.

Weight gain was a more serious problem with the atypical antipsychotics than a conventional agent in a study conducted by Dr. Wirshing and colleagues.[17] The major responsible factors are their 5-HT_{2C} and H_1 blockade, Dr. Wirshing indicated. The most important may be hypothalamic 5-HT_{2C} antagonism, which causes patients to overeat significantly. Mice deficient in the gene that encodes for 5-HT_{2C} receptors have an absence of these receptors, and they overeat and become hugely obese.[18]

Antihistaminic potency varies among atypical agents, but all have more H_1 antagonism than clinicians are accustomed to seeing, Dr. Wirshing commented. Intestinal-H_1 blockade decreases satiety feedback so that patients tend to overeat.[19] Antihistaminic action also causes sedation, which leads to increased sleep and reduced basal metabolic rate. With clozapine, for example, patients sleep 60 to 90 minutes more per day, on average. Older obese patients do not seem to be as susceptible to weight gain as other patients, Dr. Wirshing noted.

Finally, Dr. Wirshing described a test of the hypothesis that atypical agents are subjectively more tolerable than conventional agents because they cause fewer EPS. A corollary hypothesis was that an agent such as risperidone required less anticholinergic medication and thus would improve neurocognitive performance, unlike conventional agents.

Dr. Wirshing and colleagues used Awad's Drug Attitude Inventory Scale[20] in a trial of risperidone (N = 34) versus haloperidol (N = 33) in unresponsive schizophrenia patients.[21] A placebo wash-in period was followed by 4 weeks of 6 mg/day of risperidone or 15 mg/day of haloperidol, followed by 4 weeks of flexible doses of risperidone (3–15 mg/day) or haloperidol (5–30 mg/day). Dr. Wirshing reported that risperidone was significantly ($p < .006$) more tolerable than haloperidol across the entire study group.

Although risperidone causes little or no dysphoria in most patients, a curious characteristic of this and, probably, all the newer compounds is that a few patients suffer more severe dysphoria than the most dysphoric haloperidol patients, Dr. Wirshing pointed out. The dysphoria is unrelated to the presence or absence of EPS. In the study cited above, about 15% of risperidone patients were more dysphoric than the most dysphoric haloperidol patients.

Responding to a questioner, Dr. Wirshing commented that risperidone may pose a risk for neuroleptic malignant syndrome[22]—it is still too early to tell—and it is debatable whether clozapine does also.[23]

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Cost Effectiveness of the New Versus Older Antipsychotic Medications

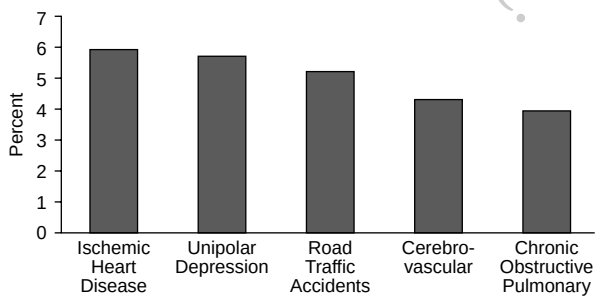
Interest in neuropsychiatric cost research or pharmacoeconomics has been growing over the past 5 or 6 years and will continue to expand, Dr. Richard J. Wyatt reported. It is likely that better studies in the next few years will demonstrate decreased hospitalizations and improved quality of life, and the savings in health care costs will compensate for the increased costs of newer medications for schizophrenia.

In the 1993 World Bank study of the worldwide burden of disease, neuropsychiatric illnesses were third (7%) behind respiratory infection (9%) and diarrheal diseases (7.5%), followed by cancer and cerebrovascular and ischemic heart disease.[1] However, Dr. Wyatt noted, in a recent World Health Organization (WHO) projection of worldwide illness for the year 2020, the 2 most costly diseases to treat will be ischemic heart disease and unipolar depression (Figure 1).[2] This result was unanticipated by the WHO and the World Bank, as evidenced by their past investments in non-neuropsychiatric illnesses and should help change how future investments are made.

In 1992, Rice and Miller[3] estimated the yearly direct and indirect costs of schizophrenia as roughly $34 billion. Dr. Wyatt and colleagues[4] were much more inclusive in terms of indirect costs and estimated the yearly costs of schizophrenia in 1991 to be approximately $65 billion.

Direct costs of schizophrenia include hospital outpatient and inpatient

Figure 1. Percentages of the Total Burden of Disease, 2020*



*Data from Murray and Lopez.[2]

costs. Dr. Wyatt estimated that, in 1991, inpatient costs were close to $11 billion per year and outpatient costs were a little over $1 billion (Table 1).[4] Private hospitals accounted for $625 million in costs and state and county mental hospitals (where most schizophrenic patients reside or are hospitalized) close to $6 billion. The Veterans Administration spent $510 million per year on patients diagnosed with schizophrenia. The direct costs not related to treatment included $2 billion per year for crime (where a person with schizophrenia committed the crime), $190 million per year for suicide, and $70 million per year for research and training.

Indirect costs for schizophrenia totaled about $46.5 billion. This included the lost productivity costs listed in Table 2: $23 billion per year for lost compensation and $4.5 billion per year for lost productivity from homemakers, a group that is not officially factored into the country's productivity, but whose functional worth to family care can be estimated, according to Dr. Wyatt. Schizophrenics in institutions cost about $4.5 billion per year. In lost productivity, schizophrenia costs the world approximately 2% to 3% of its potential productivity—4% to 5% if bipolar illness is included.

The proportions of hospital beds that were occupied by patients with schizophrenia were also calculated by Dr. Wyatt and colleagues: 11.4% of nursing home beds, 8.8% of total hospital beds, and 40.3% of total mental health beds.

Most studies that have compared atypical and conventional antipsychotics have serious drawbacks, Dr. Wyatt noted. Some did not include dropouts, or they used recall data (the investigators asked patients how they fared in the past), or patients may not have been representative. Studies of comparative hospitalization rates may be misleading since most schizophrenia patients do not require substantial hospitalization. Moreover, the criteria for hospitalization and the management of hospitalized patients have changed during the years those studies were conducted. Thus, some of the treatment benefits found in before and after mirror-image studies may be due to other factors besides the introduction of new antipsychotic agents.

Dr. Wyatt observed that all studies showed that the atypical agents were associated with lower hospitalization rates and longer hospitalization-free periods compared with conventional neuroleptics.[5–13] However, the studies are difficult to compare since they did not use the same outcome measures and most did not directly compare different atypical agents.

One study[14] suggested that clozapine treatment decreases annual hospitalization by 100 days per patient and may yield substantial economic savings. Dr. Wyatt explained that such savings are not necessarily realized. Large reductions in hospitalization may lead to steeply increased costs of outpatient services that had been provided during hospitalization.

In order to reduce important hospitalization costs, one must be able to close an entire ward, Dr. Wyatt noted. A ward must remain open even if there is only 1 patient in the ward and that patient is receiving an atypical agent. Large institutions, or federal or state government-run institutions, may be able to close entire wards and have substantial savings, whereas community hospitals might only save in overtime costs.

Dr. Wyatt also pointed out that large savings in hospitalization costs may be negated to some extent by increased outpatient costs, whereas much smaller reductions may lead to greater savings if they do not require large increases in outpatient services. In comparing risperidone and haloperidol, for example, Dr. Wyatt calculated that an annual reduction in hospitalization of 5 days per patient might pay the additional yearly cost of risperidone. This conclusion was based on the assumptions that generic haloperidol is so inexpensive it is virtually free, while risperidone (4–6 mg/day) costs approximately $1500 to $2200 per year per patient, although it would be less for doses of 1 to 3 mg/day.

Stronger evidence one way or another for cost savings will emerge in the next few years, Dr. Wyatt indicated. He predicted that the better studies will show greater than 4-day or 5-day annual reductions per patient in hospitalization. The economics of atypical agents are easier to determine and communicate than the improved quality of life that atypical agents may offer, Dr. Wyatt pointed out. Nevertheless, more people may be able to accept improved quality of life than cost savings, but this has proved difficult to measure.

To a questioner, Dr. Wyatt replied that as yet no data have shown if atypical agents improve the course of

Table 1. Direct Treatment-Related Costs of Schizophrenia, 1991*

Area	$ millions
Total inpatient	10,820
Total outpatient	1,200
Nursing home, intermediate, domiciliary care	150
Shelters	410
Substance abuse	300

*Data from Wyatt et al.[4]

Table 2. Costs of Lost Productivity Resulting From Schizophrenia, 1991*

Variable	$ millions
Homemakers	4,500
Institutions	4,500
Suicide	7,000
Family	7,000
Lost compensation	23,000

*Data from Wyatt et al.[4]

schizophrenia. His own experience is that treating patients early does improve the long-term outlook for some patients. How early is still a research issue.

Should schizophrenia be treated in the prodromal phase? Large-scale, long-term treatment in the prodromal phase would be problematic with conventional neuroleptics, particularly because of such long-term side effects as tardive dyskinesia, Dr. Wyatt stated. If, in fact, atypical agents have little or no tardive dyskinesia risk, clinicians might be more willing to expose large populations to treatment with these agents. Clinicians might be even more willing to treat in the prodromal phase if they knew how long to treat patients who have not even been identified with a first-episode.

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SYMPOSIA AND PRESENTERS

These highlight 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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