The Efficacy of Atypical Antipsychotics in the Treatment of Depressive Symptoms, Hostility, and Suicidality in Patients With Schizophrenia

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Depressive symptoms and syndromal depression commonly occur in patients with schizophrenia. Schizophrenia is also associated with aggression directed at self and others. For this article, the available literature regarding the efficacy of clozapine, risperidone, olanzapine, quetiapine, and ziprasidone in the treatment of depression, hostility, and suicidality in patients with schizophrenia was reviewed. These studies suggest that atypical antipsychotics may exert therapeutic effects on depression and hostility as well as psychosis and that clozapine and olanzapine may reduce suicidality in patients with schizophrenia. These therapeutic actions appear to represent additional advantages of atypical antipsychotics compared with standard agents. *(J Clin Psychiatry 2000;61[suppl 3]:4–9)*

The co-occurrence of depression or depressive symptoms is common in patients with schizophrenia, with estimates of the prevalence of syndromal depression in clinical populations ranging from 25% to 60%.[1–5] Epidemiologic data from community surveys confirm that these elevated prevalence rates are not merely an artifact of treatment seeking. For example, in the Epidemiologic Catchment Area (ECA) study, patients who met DSM-III criteria for schizophrenia were 28.5 times more likely to have concurrent DSM-III major depression than the general population.[6,7] Similarly, in the National Comorbidity Study (NCS), 59% of patients with schizophrenia met DSM-III-R criteria for major or minor depression.[8] Furthermore, depression does not appear to occur exclusively as a reaction to the course of chronic schizophrenia, because depressive signs and symptoms are also common among patients experiencing a first episode.[9] Co-occurring depressive signs and symptoms are of great prognostic significance since they are associated with compromised quality of life and increased risk of psychotic relapse and suicide.[10,11] Thus, recognition and treatment of depression in patients with schizophrenia are of great clinical importance.

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In addition to the recognition that depression is common in patients with schizophrenia, recent data also indicate an association between schizophrenia and violence—both suicidal and directed at other individuals.[12] An estimated 10% of patients with schizophrenia commit suicide.[13,14] Not surprisingly, suicidal ideation, suicide attempts, and suicide have been found to be associated with co-occurring depression.[15–19]

Several lines of evidence support an association between schizophrenia and violence toward others. First, a significant association between schizophrenia and violence was confirmed in 2 cross-sectional studies in community samples.[20,21] Second, in comparative studies of illness and offending behaviors, patients with schizophrenia displayed different patterns of violent behavior compared with individuals without a psychotic illness.[22–26] Furthermore, in 2 of these studies, the onset of violent behavior almost always followed the onset of illness.[24,25] Third, among symptoms of psychosis, the presence of delusions has been specifically linked to an increased risk of violence.[27,28]

Other research findings suggest that violence committed by patients with schizophrenia may, in many instances, be preventable. In one study, over 50% of patients hospitalized for a first episode of schizophrenia who had threatened others had displayed overt signs of illness for over a year.[29,30] Moreover, violent offenses committed by persons with schizophrenia often occur within the first few months of hospital discharge and by patients with established histories and contact with treaters.[25,31] In short, depression, hostility, and suicide commonly occur in patients with schizophrenia and present important target behaviors for acute and preventative treatment.

The new atypical antipsychotics have a number of advantages over conventional agents. These include lower rates of neurologic and, for some agents, neuroendocrinologic side effects and improved efficacy in the treatment of negative symptoms.[32] Emerging data also suggest that these agents may have favorable effects on depressive signs and symptoms, hostility, and suicidality in patients with schizophrenia. These new data regarding the impact of treatment with clozapine, risperidone, olanzapine, quetiapine, and ziprasidone on depressive symptoms, hostility, and suicidality are reviewed below.

TREATMENT OF DEPRESSIVE SIGNS AND SYMPTOMS

A number of recent studies suggest that clozapine is effective for patients with treatment-refractory schizoaffective disorder and psychotic mood disorders as well as treatment-refractory schizophrenia.[33–38] Moreover, clozapine appeared to exert mood-stabilizing thymoleptic properties in these reports.

Clozapine's effects on depressive symptoms in patients with chronic psychoses have been examined primarily in schizoaffective disorder.[39] Three retrospective studies of long-term response to clozapine across different diagnostic groups found that patients with schizoaffective disorder (both bipolar and depressive subtypes) displayed higher response rates than did patients with schizophrenia.[33,34,40] However, in one of these studies,[34] the presence of depressive symptoms predicted poor response to clozapine. This finding may have been due to an especially poor response in patients with major depression with psychotic features and to the substantially lower clozapine doses that these patients received compared with other patient groups. Overall, the findings from these studies, although promising, must be considered preliminary. None of these studies were prospective, randomized controlled trials, and, in many instances, clozapine was administered in combination with other psychotropic agents. Nevertheless, these early findings with clozapine were the first to suggest that atypical antipsychotics may possess thymoleptic properties in addition to their antipsychotic activity.[33]

The efficacy of risperidone in the treatment of depression in patients with schizophrenia has been examined in 3 controlled trials.[41–43] In the first study, 339 patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder were randomly assigned to risperidone (N = 167; mean ± SD dosage = 7.2 ± 2.7 mg/day) or olanzapine (N = 172; mean ± SD dosage = 17.2 ± 3.6 mg/day) treatment in an international, multicenter, double-blind, parallel-group, 28-week prospective trial.[41] Olanzapine-treated patients exhibited statistically significantly greater improvement measured by reduction of the Positive and Negative Syndrome Scale (PANSS) depression item compared with risperidone-treated patients. However, response was not separately analyzed by diagnostic group.

In the second study, the efficacy of risperidone (mean dosage = 6.9 mg/day) was compared with the combination of haloperidol (9 mg/day) and amitriptyline (180 mg/day) in an acute, 6-week trial in 123 patients with co-occurring depressive and psychotic symptoms.[42] This study included patients who had schizophrenia with depressive symptoms; schizoaffective disorder, depressive type; and major depression with psychotic features. Patients in each treatment group who completed at least 3 weeks of pharmacotherapy displayed marked reductions in measures of depression and psychosis. However, the reductions in the Brief Psychiatric Rating Scale (BPRS) and Beck-Rafaelson Melancholia Scale total scores in the overall group of patients were significantly greater in the haloperidol/amitriptyline group than in the risperidone group. This difference was mainly attributable to significantly greater improvement in patients with psychotic depression. There were no significant differences in improvement in either depression or psychosis between the 2 treatment groups in patients with schizoaffective disorder, depressed type or schizophrenia with depressive symptoms.

In the third controlled study, haloperidol (2–20 mg/day) was compared with risperidone (2–20 mg/day) in an 8-week trial involving 62 patients with schizophrenia (N = 49) or schizoaffective disorder (N = 13).[43] There were no significant differences between the 2 treatment groups in improvement of overall psychopathology as measured by changes in BPRS total score and percentage of patients achieving remission. Haloperidol-treated patients displayed significantly greater improvement than did risperidone-treated patients on the anxiety/depression factor of the BPRS. As anticipated, extrapyramidal side effects were lower with risperidone. This study did not specifically include patients with prominent depressive symptoms. In addition, the small sample size may have contributed to the failure to find marked differences between agents.

One other report, a case series of 10 patients treated with risperidone (mean dosage = 7.2 mg/day) in an open trial, described improvement in both depressive and psychotic symptoms.[44] Three of these 10 patients received risperidone for schizoaffective disorder, depressive type (the other 7 had psychotic depression), and all displayed substantial improvement. Finally, risperidone has been reported to improve depressive symptoms in several other case series of patients with schizoaffective disorder[45–47] and treatment-refractory depression.[48]

The efficacy of olanzapine in the treatment of depressive signs and symptoms co-occurring with schizophrenia has been examined in 2 controlled studies.[41,49] As previously described, patients who received olanzapine had a significantly greater reduction on the PANSS depression item compared with patients treated with risperidone in one

comparison trial.[41] In the second controlled study, 1996 patients with schizophrenia or schizoaffective disorder were randomly assigned to treatment with olanzapine (mean modal dosage = 13 mg/day) or haloperidol (mean modal dosage = 12 mg/day) in a double-blind, comparative trial consisting of a 6-week acute treatment interval followed by a 46-week masked responder maintenance period.[49] A surprisingly high percentage (55%) of patients displayed at least moderate depressive symptoms (defined as Montgomery-Asberg Depression Rating Scale [MADRS] scores of ≥ 16) at baseline. Although treatment with either agent was associated with short-term (6-week) improvement in MADRS scores, patients who received olanzapine had significantly greater improvement than patients who received haloperidol. Furthermore, the response rate (defined as ≥ 50% improvement in MADRS total scores after ≥ 3 weeks of treatment) for patients receiving olanzapine was also significantly greater. In a secondary analysis of the subgroup of patients with schizoaffective disorder (N = 134) who participated in this study, olanzapine produced significantly greater improvement in MADRS scores compared with haloperidol.

Of the 1996 patients who began the acute treatment trial, 933 responders to olanzapine and haloperidol entered the masked extension phase (olanzapine, N = 718; haloperidol, N = 215). By observed case plot analysis, the initial response associated with olanzapine as measured by reductions in MADRS scores persisted over the subsequent maintenance period.

Additional evidence of olanzapine's beneficial effects on depressive symptoms comes from studies in patients with schizoaffective disorder,[50] psychotic depression,[51] and treatment-refractory depression.[52,53] In the largest controlled trial ever conducted in patients with schizoaffective disorder (N = 300), patients with the depressive subtype who received olanzapine experienced significantly greater reductions in BPRS total, PANSS total, PANSS negative, Clinical Global Impressions (CGI) severity, and MADRS total scores compared with patients who received haloperidol.[50]

In a retrospective case-control study of inpatients with psychotic depression, the response of olanzapine-treated patients (N = 15) was compared with the response of patients treated with typical antipsychotics (N = 15).[51] The majority (80%) of patients in each group also received antidepressants. Ten (67%) of the 15 patients who received olanzapine were much or very much improved at discharge compared with 4 (27%) of the 15 patients treated with typical antipsychotics.

Two recent reports described improvement in patients with nonpsychotic treatment-refractory major depressive disorder treated with olanzapine.[52,53] One of these studies consisted of an 8-week, double-blind, 2-site trial designed to assess the safety and efficacy of olanzapine (5–20 mg/day) and fluoxetine (20–60 mg/day), alone and in combination, in the treatment of 28 patients with nonpsychotic treatment-refractory depression.[52] Patients who received the combination exhibited rapid (by 1 week) and significantly greater improvement in MADRS and CGI total scores than patients receiving either medication alone. There were no significant differences in adverse events among the 3 treatment groups, suggesting that the combination was well tolerated.

To our knowledge, only one brief report is available regarding the effects of quetiapine on depressive signs and symptoms in patients with schizophrenia.[54] In an analysis of data from 2 double-blind, 6-week acute treatment trials comparing improvement in BPRS factor I scores (mean of items for depressive mood, guilt feelings, somatic concern, and anxiety) and BPRS mood cluster scores (mean of items for depressive mood, guilt feelings, anxiety, and tension) were examined among patients receiving quetiapine across a variety of doses, haloperidol, or placebo. In both trials, quetiapine was superior to placebo in improving depressive symptoms, but haloperidol was not. Furthermore, depressive symptoms were improved in a significantly greater proportion of patients treated with quetiapine compared with haloperidol or placebo.

Preliminary data from 2 controlled trials suggest that ziprasidone improves depressive symptoms in patients with schizophrenia or schizoaffective disorder.[55,56] In an analysis of improvement in depressive symptoms in patients with schizophrenia or schizoaffective disorder who had clinically significant depressive symptoms at baseline (defined as MADRS total score ≥ 14), improvement at 6 weeks in patients who received ziprasidone, 160 mg/day, was significantly greater than that in patients who received placebo.[55] In a similar analysis of data from another placebo-controlled, double-blind, 4-week acute treatment trial, improvement in the BPRS anxiety-depression cluster among patients with clinically significant symptoms at baseline (defined as BPRS anxiety-depression cluster score ≥ 18) was significantly greater in patients receiving ziprasidone, 120 mg/day, compared with placebo.[56] These data suggest that ziprasidone, at doses of 120 and 160 mg/day, exerts antidepressant activity in patients with schizophrenia or schizoaffective disorder who have at least moderate symptoms of depression at baseline.

TREATMENT OF HOSTILITY, AGGRESSION, AND VIOLENCE

Hostility and aggressive behavior (including overt acts of violence) can result from psychosis, particularly when patients perceive themselves as threatened as a manifestation of thought disorder or persecutory delusion.[56] Although typical antipsychotics ameliorate psychosis, anxiety, and agitation in many patients, they do not appear to have specific antiaggressive activity.[57,58] Furthermore, side effects of typical antipsychotics such as akathisia often complicate the management of aggressive behavior in pa-

tients with schizophrenia and may contribute to worsening of hostility.[58]

A number of reports suggest that clozapine, unlike typical antipsychotics, may exert specific therapeutic effects on aggressive behavior.[59–65] All of these reports consist of open trials and include patients in forensic[60,61] and nonforensic[62–68] settings. These reports also vary according to diagnostic criteria used, duration of treatment, and outcome measures. Nevertheless, the patients described in nearly all these reports were severely and chronically ill and refractory to prior treatment. These studies all found a substantial reduction in hostile, aggressive, and violent behavior in a significant number of patients.

Three reports have described the effect of risperidone in the treatment of hostility,[69] aggression,[58] and violence[70] in patients with schizophrenia. The first study compared changes in the hostility item of the PANSS in 139 patients with schizophrenia who received risperidone, haloperidol, or placebo in a 9-week, double-blind, multicenter acute treatment trial.[69] Overall, risperidone exerted a greater selective (unrelated to change in psychosis) improvement in hostility than haloperidol or placebo. Patients in this study did not represent a population selected for aggressive or violent behavior. In the second study, the effect of risperidone on aggression was assessed by comparing data regarding seclusion and restraint in a state hospital population of patients with refractory schizophrenia 6 months prior to and during treatment with risperidone.[58] Risperidone-treated patients were also compared with a matched group treated with typical antipsychotics. Improvement in aggression occurred during the observed time period and was comparable in both treatment groups. In the third study, the effects of risperidone on aggression were compared with those of typical antipsychotics in a severely ill, forensic group of patients with schizophrenia and recent histories of violence.[70] No significant differences in clinical functioning or aggressive behaviors were observed between treatment groups, and overall treatment response was poor.

The effects of olanzapine on agitation and aggression have been examined in patients with schizophrenia[71] and in patients with Alzheimer's disease.[72] In a comprehensive analysis of data from double-blind acute and long-term trials as well as open-label extension trials following 4 multicenter, controlled studies, the incidence of aggression was examined in patients with DSM-III-R schizophrenia, schizophreniform, or schizoaffective disorder treated with olanzapine (N = 2284), haloperidol (N = 810), or placebo (N = 112).[71] Data analyzed included adverse event reports and rating scale items from the BPRS and MADRS. There were no significant differences among olanzapine, haloperidol, and placebo in the incidence of externally directed aggression as captured by adverse event reports. Patients receiving olanzapine and haloperidol had significant reductions in mean hostility scores on the BPRS compared with those receiving placebo.

Two studies have assessed the efficacy of quetiapine in reducing hostility in patients with schizophrenia.[73,74] Both studies included patients who participated in double-blind, randomized clinical trials in nonforensic settings. In the first study, a 6-week, multicenter trial, patients received quetiapine (75–750 mg/day) or placebo and treatment effects on hostility were assessed by changes in the BPRS factor V scores (hostility, suspiciousness).[73] There were no significant differences between quetiapine and placebo in BPRS factor V scores over the course of this 6-week trial. In contrast, quetiapine (600 mg/day) was superior to placebo in reducing hostility and aggression as assessed by changes in the BPRS factor V score, the BPRS hostility item, and BPRS hostility cluster score (mean of anxiety, tension, hostility, suspiciousness, uncooperativeness, excitement) in a second 6-week, double-blind, placebo-controlled trial.[74]

Although the efficacy of ziprasidone in reducing hostility and aggression has not yet been studied, 2 studies have reported on the efficacy of intramuscular ziprasidone in ameliorating agitation.[75,76] In the first study, 132 patients with a nonorganic acute psychosis were randomly assigned to 3 days of treatment with i.m. ziprasidone (maximum, 80 mg/day) followed by 4 days of oral ziprasidone (80–200 mg/day) or i.m. haloperidol (maximum, 40 mg/day) followed by oral haloperidol (10–80 mg/day).[75] Mean BPRS scores improved with both ziprasidone and haloperidol. As anticipated, the incidence of neurologic side effects was significantly lower in the ziprasidone group. In the second study, 79 patients with acute psychosis (schizophrenia, schizoaffective disorder, or bipolar or psychotic disorder not otherwise specified) and agitation were randomly assigned to receive an initial dose of ziprasidone, 2 mg or 20 mg i.m., followed by up to 3 subsequent identical doses a minimum of 4 hours apart as needed in a 24-hour acute response trial.[76] Ziprasidone 20 mg i.m. was superior to 2 mg i.m. at reducing agitation within 2 hours of initial administration. In neither study were data specifically presented regarding reduction in hostility, and in both studies, patients were in nonforensic settings.

IMPACT ON SUICIDALITY

The impact of antipsychotic agents in general, and of atypical antipsychotics in particular, on suicide in patients with schizophrenia has been little studied.[77] Findings from 2 recent studies indicate that clozapine decreases suicidality in patients with treatment-refractory schizophrenia.[78,79] In the first study, prior episodes of suicidality were assessed in 237 neuroleptic-responsive and 184 neuroleptic-refractory patients with schizophrenia or schizoaffective disorder. Eighty-eight of the neuroleptic-refractory patients received clozapine and were prospectively evaluated for suicidality for periods ranging from 6 months to 7 years.[78] During clozapine treatment, suicidality was eliminated in 10 of 13 patients who had made > 1

prior attempt and the number of suicide attempts with a high probability of lethality decreased from 5 to 0. There was an overall 86% reduction in suicide attempts with clozapine treatment, and this decrease in suicidality was associated with reductions in both depressive symptoms and hopelessness. In the second study, clozapine's effects on mortality were assessed by comparing rates of various causes of death in 67,072 patients who had received (but discontinued) or were presently treated with clozapine.[79] Mortality from suicide was significantly reduced in patients receiving clozapine compared with those who had discontinued the agent (rate ratio [RR] = 0.17, 95% confidence interval [CI] = 0.10 to 0.30).

Two analyses to date have provided data regarding the impact of treatment with olanzapine on suicidality in patients with schizophrenia or schizoaffective disorder.[71,80] In the previously described data analysis from multiple clinical trials of olanzapine,[71] the incidence of self-directed aggression among patients receiving olanzapine, haloperidol, and placebo, based on adverse event reports, was not significantly different. Analyses of the MADRS suicidal thoughts item from these trials indicated significantly greater improvement in suicidal thoughts in patients receiving olanzapine compared with haloperidol.

The beneficial effect of olanzapine, compared with haloperidol, on suicidality in patients with chronic psychoses was also borne out in an analysis of treatment extending to 1 year.[80] In this analysis, a 2.3-fold reduction in the annual suicide attempt rate, as measured at baseline and again at endpoint, occurred in patients receiving olanzapine compared with haloperidol. These findings are similar to those associated with clozapine, described above.[78] To our knowledge, there are no other data available at the present time regarding the impact of other atypical antipsychotics on suicidality in patients with schizophrenia.

CONCLUSION

The available data suggest that the broad group of atypical antipsychotics may exert therapeutic effects on depressive as well as psychotic symptoms. This therapeutic action appears to represent an additional advantage of atypical agents compared with standard antipsychotics (neuroleptics). Preliminary data also suggest that atypical antipsychotics may ameliorate hostility and aggressive behaviors associated with psychosis. Finally, studies suggest that treatment with clozapine or olanzapine may significantly reduce suicidality in patients with schizophrenia.

Drug names: amitriptyline (Elavil and others), clozapine (Clozaril), fluoxetine (Prozac), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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REFERENCES

1. Siris SG. Depression and schizophrenia. In: Hirsch SR, Weinberger DR, eds. Schizophrenia. Oxford, England: Blackwell Science; 1995:128–145
2. Hirsch ST, Jolley AG. The dysphoric syndrome in schizophrenia and its implications for relapses. Br J Psychiatry 1989;155(suppl 5):45–50
3. Johnson DAW. The significance of depression in the prediction of relapse in chronic schizophrenia. Br J Psychiatry 1988;152:320–323
4. Martin RL, Cloninger CR, Guze SB, et al. Frequency and differential diagnosis of depressive syndromes in schizophrenia. J Clin Psychiatry 1985;46 (11, sec 2):9–13
5. Harrow M, Yonan CA, Sands JR, et al. Depression in schizophrenia: are neuroleptics, akinesia, or anhedonia involved? Schizophr Bull 1994;20: 327–338
6. Robins LN, Regier DA, eds. Psychiatric Disorders in America: The Epidemiologic Catchment Area Study. New York, NY: The Free Press; 1991
7. Strakowski SM. The co-occurrence of depression in schizophrenia. In: Keck PE Jr, ed. Managing the Depressive Symptoms of Schizophrenia. London, England: Science Press. In press
8. Judd LL. Mood disorders in schizophrenia: epidemiology and comorbidity. J Clin Psychiatry Monograph 1998;16(1):2–4
9. Koreen AR, Siris SG, Chakos M, et al. Depression in first-episode schizophrenia. Am J Psychiatry 1993;150:1643–1648
10. Birchwood M, Mason R, MacMillan F, et al. Depression, demoralization and control over psychotic illness: a comparison of depressed and non-depressed patients with a chronic psychosis. Psychol Med 1993;23: 387–395
11. Roy A, Thompson R, Kennedy S. Depression in chronic schizophrenia. Br J Psychiatry 1983;142:465–470
12. The Special Hospitals Treatment Resistant Schizophrenia Research Group. Schizophrenia, violence, clozapine and risperidone: a review. Br J Psychiatry 1996;169(suppl 31):21–30
13. Miles C. Conditions predisposing to suicide: a review. J Nerv Ment Dis 1977;164:221–246
14. Caldwell CB, Gottesman H. Schizophrenics kill themselves too: a review of risk factors for suicide. Schizophr Bull 1990;16:571–589
15. Roy A. Suicide in chronic schizophrenia. Br J Psychiatry 1982;141: 171–177
16. Roy A. Depression, attempted suicide, and suicide in patients with chronic schizophrenia. Psychiatr Clin North Am 1986;9:193–206
17. Drake RE, Cotton PG. Depression, hopelessness and suicide in chronic schizophrenia. Br J Psychiatry 1986;148:554–559
18. Prasad AJ, Kumar N. Suicidal behavior in hospitalized schizophrenics. Suicide Life Threat Behav 1988;18:265–269
19. Barnes TR, Curson DA, Liddle PE, et al. The nature and prevalence of depression in chronic schizophrenic in-patients. Br J Psychiatry 1989;154: 486–491
20. Swanson JW, Holzer CE, Ganju VK, et al. Violence and psychiatric disorder in the community: evidence from the Epidemiologic Catchment Area Surveys. Hosp Community Psychiatry 1990;41:761–770
21. Link B, Andrews H, Cullen FT. The violent and illegal behavior of mental patients reconsidered. Am Suicide Rev 1992;57:275–292
22. Lindqvist P, Allbeck P. Schizophrenia and crime: a longitudinal follow-up of 644 schizophrenics in Stockholm. Br J Psychiatry 1990;159:345–350
23. Hodgins S. Mental disorder, intellectual deficiency and crime. Arch Gen Psychiatry 1992;49:476–483
24. Coid B, Lewis S, Reveley AM. A twin study of psychosis and criminality. Br J Psychiatry 1993;163:87–92
25. Taylor PJ. Schizophrenia and crime: distinctive patterns in association. In: Hodgins S, ed. Crime and Mental Disorder. Beverly Hills, Calif: Sage; 1993:63–85
26. Wessely SC, Castle D, Douglas AJ, et al. The criminal careers of incident cases of schizophrenia. Psychol Med 1994;24:483–502
27. Taylor PJ. Motives for offending among violent and psychotic men. Br J Psychiatry 1985;147:491–498
28. Link B, Stueve A. Psychiatric symptoms and the violent/illegal behavior of mental patients compared to community controls. In: Monahan J, Steadman H, eds. Violence and Mental Disorder. Chicago, Ill: University of Chicago Press; 1994
29. Johnstone EC, Crow TJ, Johnson AL, et al. The Northwick Park Study of first episode of schizophrenia. Br J Psychiatry 1986;148:115–143
30. Humphreys HS, Johnstone EC, MacMillan JF, et al. Dangerous behavior preceding first admission for schizophrenia. Br J Psychiatry 1992;161:

501–505
31. Taylor PJ, Gunn J. Violence and psychosis. BMJ 1984;288:1945–1949
32. Keck PE Jr, McElroy SL. The new antipsychotics and their therapeutic potential. Psychiatr Ann 1997;27:320–331
33. McElroy SL, Dessain EC, Pope HG Jr, et al. Clozapine in the treatment of psychotic mood disorders, schizoaffective disorder, and schizophrenia. J Clin Psychiatry 1991;52:411–414
34. Banov MD, Zarate CA Jr, Tohen M, et al. Clozapine therapy in refractory affective disorders: polarity predicts response in long-term follow-up. J Clin Psychiatry 1994;55:295–300
35. Calabrese JR, Kimmel SE, Woyshville MJ, et al. Clozapine for treatment-refractory mania. Am J Psychiatry 1996;153:759–764
36. Suppes T, McElroy SL, Gilbert J, et al. Clozapine in the treatment of dysphoric mania. Biol Psychiatry 1992;32:270–280
37. Suppes T, Phillips KA, Judd DR. Clozapine treatment of nonpsychotic rapid cycling bipolar disorder: a report of three cases. Biol Psychiatry 1994;36: 338–340
38. Zarate CA Jr, Tohen M, Baldessarini RJ. Clozapine in severe mood disorders. J Clin Psychiatry 1995;56:411–417
39. Keck PE Jr, McElroy SL, Strakowski SM, et al. Pharmacologic treatment of schizoaffective disorder. Psychopharmacology (Berl) 1994;114:529–538
40. Naber D, Hippius H. The European experience with the use of clozapine. Hosp Community Psychiatry 1990;41:886–890
41. Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997;17:407–418
42. Müller-Seicheneder F, Müller MJ, Hillert A, et al. Risperidone versus haloperidol and amitriptyline in the treatment of patients with a combined psychotic and depressive syndrome. J Clin Psychopharmacol 1998;18: 111–120
43. Ceskova E, Svestka J. Double-blind comparison of risperidone and haloperidol in schizophrenic and schizoaffective psychoses. Pharmacopsychiatry 1993;26:121–124
44. Hillert A, Maier W, Wetzel H, et al. Risperidone in the treatment of disorders with combined psychotic and depressive syndrome: a functional approach. Pharmacopsychiatry 1992;25:213–217
45. Dwight MM, Keck PE Jr, Stanton SP, et al. Antidepressant activity and mania associated with risperidone treatment of schizoaffective disorder. Lancet 1994;344:554–555
46. Keck PE Jr, Wilson DR, Strakowski SM, et al. Clinical predictors of acute risperidone response in schizophrenia, schizoaffective disorder, and psychotic mood disorders. J Clin Psychiatry 1995;56:466–470
47. Sajatovic M, DiGiovanni SK, Bastani B, et al. Risperidone therapy in the treatment of refractory acute bipolar and schizoaffective mania. Psychopharmacol Bull 1996;32:55–61
48. O'Conner M, Silver H. Adding risperidone to selective serotonin reuptake inhibitor improves chronic depression [letter]. J Clin Psychopharmacol 1998;18:89–91
49. Tollefson GD, Sanger TM, Lu Y, et al. Depressive signs and symptoms in schizophrenia. Arch Gen Psychiatry 1998;55:250–258
50. Tollefson GD, Beasley CM Jr, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective disorder and schizophreniform disorder: results of the international collaborative trial. Am J Psychiatry 1997;154:457–465
51. Rothschild AJ, Bates KS, Boehringer K, et al. Olanzapine response in psychotic depression. In: Scientific Abstracts of the 36th Annual Meeting of the American College of Neuropsychopharmacology; Dec 10, 1997; Honolulu, Hawaii
52. Shelton R, Tollefson G, Tohen M, et al. The study of olanzapine plus fluoxetine in treatment-resistant major depressive disorder without psychotic features. In: Abstracts of the 38th Annual Meeting of the New Clinical Drug Evaluation Unit; June 10–11, 1998; Boca Raton, Fla
53. Weisler RH, Ahearn EP, Davidson JR, et al. Adjunctive use of olanzapine in mood disorders: five case reports. Ann Clin Psychiatry 1997;9:259–262
54. Arvanitis LA, Miller BG, Kowalcyk BB, et al. Efficacy of "Seroquel" (quetiapine fumerate) in affective symptoms of schizophrenia. In: Scientific Abstracts of the 36th Annual Meeting of the American College of Neuropsychopharmacology; Dec 8, 1997; Honolulu, Hawaii
55. Keck PE Jr, Harrigan EP, Reeves KR. The efficacy of ziprasidone in schizophrenia and schizoaffective disorder: an update [abstract]. Biol Psychiatry 1997;42(suppl):42S
56. Keck PE Jr, Reeves KR, Harrigan EP. Ziprasidone: an overview of efficacy and tolerability in the treatment of patients with acute exacerbation of schizophrenia or schizoaffective disorder. In: Abstracts of the 37th Annual Meeting of the New Clinical Drug Evaluation Unit; May 27–30, 1997; Boca Raton, Fla
57. Fava M. Psychopharmacologic treatment of pathologic aggression. Psychiatr Clin North Am 1997;20:427–450
58. Buckley PF, Ibrahim ZY, Singer B, et al. Aggression and schizophrenia: efficacy of risperidone. J Am Acad Psychiatry Law 1997;25:173–181
59. Balassa M, Deisenhammer E, Schever H. Clozapine, ein nicht ketaleptagenes neuroleptikum, in der behandlung von verhaltenssturngen mit erregangszustanden. Wiener Med Wachenschrift 1971;121:90–92
60. Maier GJ. The impact of clozapine on 25 forensic patients. Bull Am Acad Psychiatry Law 1992;20:297–307
61. Ebrahim GM, Gibler B, Gacono CB, et al. Patient response to clozapine in a forensic psychiatric hospital. Hosp Community Psychiatry 1994;45: 271–273
62. Chiles JA, Davidson P, McBride D. Effects of clozapine on use of seclusion and restraint at a state hospital. Hosp Community Psychiatry 1994;45: 269–271
63. Wilson WH. Clinical review of clozapine treatment in a state hospital. Hosp Community Psychiatry 1992;43:700–703
64. Ratey JJ, Leveroni C, Kilmer D, et al. The effects of clozapine on severely aggressive psychiatric inpatients in a state hospital. J Clin Psychiatry 1993; 54:219–223
65. Buckley P, Bartell J, Donenwirth K, et al. Violence and schizophrenia: clozapine as a specific antiaggressive agent. Bull Am Acad Psychiatry Law 1995;23:607–611
66. Spivak B, Mester R, Wittenberg N, et al. Reduction of aggressiveness and impulsiveness during clozapine treatment in chronic neuroleptic-resistant schizophrenic patients. Clin Neuropharmacol 1997;20:442–446
67. Hector RI. The use of clozapine in the treatment of aggressive schizophrenia. Can J Psychiatry 1998;43:466–472
68. Rabinovitz J, Avnon M, Rosenberg V. Effect of clozapine on physical and verbal aggression. Schizophr Res 1996;22:249–255
69. Czobor P, Volavka J, Meibach R. Effect of risperidone on hostility in schizophrenia. J Clin Psychopharmacol 1995;15:243–249
70. Beck NC, Greenfield SR, Gotham H, et al. Risperidone in the management of violent, treatment-resistant schizophrenics hospitalized in a maximum security forensic facility. J Am Acad Psychiatry Law 1997;25:461–468
71. Beasley CM, Sayler ME, Kiesler GM, et al. The influence of pharmacotherapy on self-directed and externally-directed aggression in schizophrenia [abstract]. Schizophr Res 1998;29:28
72. Street J, Mitan S, Tamura R, et al. Olanzapine in the treatment of psychosis and behavioral disturbances associated with Alzheimer's disease. Presented at the 3rd Congress of the European Federation of Neurological Societies; Sept 19–25, 1998; Seville, Spain
73. Borison RL, Arvanitis LA, Miller BG, et al. ICI 204, 636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. J Clin Psychopharmacol 1996;16:158–169
74. Cantillon M, Arvanitis LA, Miller BG, et al. "Seroquel" (quetiapine fumarate) reduces hostility and aggression in patients with acute schizophrenia. Presented at the 36th Annual Meeting of the American College of Neuropsychopharmacology; Dec 8–12, 1997; Honolulu, Hawaii
75. Brook S, Krams M, Gunn KP, et al. The efficacy and tolerability of intramuscular (i.m.) ziprasidone versus i.m. haloperidol in patients with acute, non-organic psychosis. Presented at the 10th annual meeting of the European College of Neuropsychopharmacology; Sept 1997; Austria Centre, Austria
76. Reeves KR, Swift RH, Harrigan EP. A comparison of rapid-acting, intramuscular (i.m.) ziprasidone 2 mg and 20 mg in patients with psychosis and acute agitation. Presented at the Annual Meeting of the Collegium Internationale Neuropsychopharmacologium; July 1998; Glasgow, Scotland
77. Meltzer HY. Suicide in schizophrenia: risk factors and clozapine treatment. J Clin Psychiatry 1998;59(suppl 3):15–20
78. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. Am J Psychiatry 1995;152:183–190
79. Walker AM, Lanza LL, Arellano F, et al. Mortality in current and former users of clozapine. Epidemiology 1997;8:671–677
80. Glazer WM. Formulary decisions and health economics. J Clin Psychiatry 1998;59(suppl 19):23–29