The Routine Use of Atypical Antipsychotic Agents: Maintenance Treatment

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Placebo-controlled maintenance studies of conventional antipsychotic agents demonstrate a significant reduction in the risk of schizophrenic relapse in neuroleptic-treated patients. Neuroleptic discontinuation even in patients who remained in remission for as long as 5 years results in a relapse rate comparable to that seen for patients initially assigned to placebo. Yet, patients maintained on conventional neuroleptics are exposed to the risk of tardive dyskinesia (approximately 5% per year for patients with up to 10 years of neuroleptic exposure). Attempts have been made to reduce neuroleptic exposure. A lower maintenance dose was associated with higher relapse rates, as was intermittent, targeted therapy. Psychoeducational treatment studies reaffirmed that the major influence on the rate of rehospitalization was the dose of conventional maintenance medication. Although data are scarce for maintenance treatment with atypical antipsychotic drugs, findings suggest that atypical agents are at least as efficacious and may be better tolerated. Olanzapine has demonstrated efficacy in maintenance treatment as well as a reduced risk of tardive dyskinesia compared with haloperidol.

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The modern medical miracle of the conventional antipsychotic agents was chronicled by the precipitous drop in the population of psychiatric patients in state and county hospitals in the 1950s and 1960s coincident with the advent of the phenothiazines, particularly chlorpromazine, for the treatment of mental illness. Not only the acute efficacy of antipsychotic agents but also their chronic efficacy as maintenance treatments contributed to the exodus of patients from the state hospitals. A meta-analysis of nearly 3 dozen placebo-controlled neuroleptic maintenance treatment studies demonstrated the significant advantage of neuroleptic treatment in preventing schizophrenic relapse.[1] Overall, 20% of patients on neuroleptics relapsed versus 53% on placebo after about 6 months of treatment. Furthermore, it was estimated that neuroleptics could reduce the rate of relapse by a factor of from 2.5 to 5.

BENEFITS AND RISKS OF MAINTENANCE ANTIPSYCHOTIC TREATMENT

Even though patients could relapse through their conventional antipsychotic treatment, they still may have derived an advantage from having been on the medication. Bartko et al.[2] reported that those patients who relapsed on maintenance neuroleptic treatment had an improvement coefficient, or rate of improvement during subsequent hospitalization, greater than those patients who relapsed off medication. Likewise, the length of hospital days needed for these patients to recover was significantly less if the patients were on neuroleptics when they relapsed versus if they relapsed off neuroleptics.

Although it was established that maintenance conventional antipsychotic drug treatment was essential to reducing the risk of schizophrenic relapse, it was less clear how long treatment should be continued, especially in patients who remained in remission several years while on neuroleptic treatment. A series of well-designed, controlled studies (Table 1) addressed this question.[3–8] Although these patients remained in remission for as long as 5 years, stopping their neuroleptic treatment resulted in an incidence of relapse similar to that for the placebo patients in the earlier maintenance studies. The survival rate was no greater than approximately 25%. One would think that long survival on neuroleptics, free of relapses, may have provided a filtering mechanism to determine the hardier of the patients that were less needy of continued neuroleptic treatment; this was not found to be the case.

The dilemma suggested by these studies is that schizophrenic patients are dependent on antipsychotic medication to maintain remission, yet they are also exposed to the risks of continuous neuroleptic treatment, namely, tardive dyskinesia. The incidence of tardive dyskinesia developing de novo in patients who accumulated up to 10 years of

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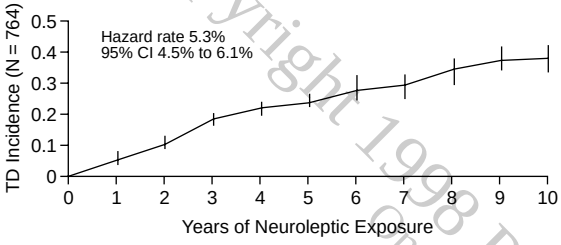
Table 1. Drug Discontinuation Among Successfully Maintained Schizophrenic Outpatients

Study	N	Time in Remission	Length of Follow-Up Off Drug	Relapse Rate[a]
Hogarty et al, 1976[3]	41	2–3 y	12 mo	65%
Johnson 1976[4]	23	1–2 y	6 mo	53%
Dencker et al, 1980[5]	32	2 y	24 mo	94%
Cheung, 1981[6]	30	3–5 y	18 mo	62%
Johnson, 1981[7]	60	1–4 y	18 mo	80%
Wistedt, 1981[8]	16	6 mo	12 mo	100%

[a]Unweighted mean = 76%.

Figure 1. Tardive Dyskinesia Incidence as Function of Neuroleptic Exposure*



*Data from reference 9.

neuroleptic exposure was found to be approximately 5% per year[9] (Figure 1). This finding is consistent with other studies reported in the literature.[10] Patients on a prolonged course of neuroleptic treatment are at significant risk of developing tardive dyskinesia.

The need to balance continued maintenance treatment to prevent relapses with limiting the risk of chronic side effects led to the second generation of maintenance neuroleptic treatment studies. These studies were specifically designed to determine if a lower effective dose of drug could maintain patients in the community free of relapses yet also lower their risk of neuroleptic side effects. Dose-response studies[11–16] employing fluphenazine decanoate or haloperidol decanoate examined the rates of relapse at up to 1 year of treatment. Across several studies, a lower dose of neuroleptic treatment was associated with the greater risk of relapse. At least 1 study[17] suggested that, although schizophrenic patients on lower doses were exposed to a greater risk of relapse, these patients had better social functioning and lower tardive dyskinesia scores than those on higher doses who had a lower risk of relapse.

Some investigators approached the high-versus-low dose dilemma by way of third-generation maintenance studies that were based on the clinical impression that psychotic episodes are preceded by a prodromal period. The strategy employed medicating patients specifically during the prodromal period to forestall or prevent the development of fully activated relapses. Patients maintained free of neuroleptic treatment until they became prodromal, at which point medication was reinstituted, were compared

Table 2. Percentage of Subjects Rehospitalized Over 2-Year Period by Medication and Family Management Conditions*

Family Management	Standard Dose	Low Dose	Targeted Dose	Total
Applied	19	26	43	29
Supportive	31	25	49	35
Total	25	25	46	32

*Data from reference 16. Dose × rehospitalization, $p < .001$; family management × rehospitalization, NS; dose × family management × rehospitalization, NS.

with patients on continuous treatment. In all 5 major studies,[6,18–21] patients on continuous treatment had less risk of relapse versus patients on intermittent, targeted therapy. Although the intermittent strategy held promise for reducing exposure to neuroleptics, it was associated with greater risk of relapse and, theoretically, may have sensitized patients for future treatment refractoriness.

PSYCHOEDUCATIONAL TREATMENT STRATEGIES

Subsequently, information learned about relapse within high "expressed emotion" households[22,23] led investigators to develop psychoeducational, family-oriented, treatment strategies that perhaps would work in combination with neuroleptics to forestall schizophrenic relapse. The Treatment Strategies in Schizophrenia Study investigated the hypothesis that reducing the stressors between schizophrenics and their significant others, educating families of patients about the disease, and giving them strategies to deal with the illness would work synergistically with medication and lead to a significant reduction in relapse.[16] Patients were randomly assigned to 3 drug groups: a continuous standard dose group (patients on fluphenazine decanoate), a continuous reduced dose group (a one-fifth dilution of standard dose fluphenazine decanoate), or an intermittent targeted drug strategy (Table 2). In addition to this 3-way randomization, all patients were randomly assigned to receive either an intensive applied family management psychoeducational intervention or a merely supportive intervention. This study reaffirmed that the major influence on whether patients were rehospitalized during the maintenance phase was the dose of medication they received. The rehospitalization rate on either the standard or low dose was significantly less than the rehospitalization rate on the intermittent or targeted therapy. Furthermore, no significant difference was noted between the family management strategies across all the drug treatments and no interaction was significant between the targeted therapy, the family management, and rehospitalization. Therefore, whether one was on medication, and not family intervention, decreased the risk of rehospitalization or relapse. It is noteworthy that the relapse rate in the groups that had either applied or supportive psychoeducational family intervention was less than

the relapse rate usually seen in a placebo group, thus suggesting the degree of efficacy of these psychotherapies.

ATYPICAL ANTIPSYCHOTICS

The fourth generation of maintenance studies looked at continuous treatment with atypical antipsychotic agents to prevent relapse as well as hospitalization without the cost of significant side effects. Unfortunately, very few data are available about maintenance treatment studies in patients who are on atypical antipsychotics, in particular, clozapine and risperidone.

Clozapine

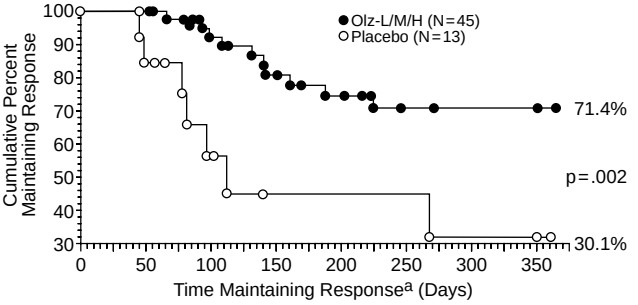
In a few small studies,[24–26] clozapine demonstrated response rates in relatively refractory patients of about 38% at 6 weeks and 60% at 6 months. These studies indicated a trend of increased response rate over time that could translate to increased maintenance treatment efficacy with clozapine.

The efficacy of clozapine for maintenance treatment was also examined in 2 mirror-image studies in which the number of relapses or hospitalizations in a cohort of patients during the year of treatment with clozapine was compared with the number of such events during the year prior to initiation of clozapine treatment. In 1 study,[24] during the year before treatment with clozapine, 79% of the patients required hospitalization, while only 21% were hospitalized during treatment. Even more dramatic was the difference in the total number of hospitalizations: 46 in the year before and only 8 during the year of clozapine treatment. Breier et al.[27] had similar results as a mean of 1.3 patients hospitalized the year prior to clozapine treatment reduced to 0.4 during the first year of clozapine treatment, and the average number of days hospitalized decreased from 32 to only 3.5. In addition, an average of 2.0 relapse events with 42.6 days relapsed was improved to 0.3 relapse events and 4.9 days relapsed during the year of clozapine treatment. More recently, Essock et al.[28] looked at patients treated with clozapine versus patients treated with usual care in a naturalistic design. As in the previous studies, clozapine had a significant effect in reducing the number of patients that required hospitalization. Of 76 patients who received clozapine, 83% did not require hospitalization during the follow-up year, as compared to 59% of the 48 patients on usual care. Although these are not the classical maintenance treatment studies that one would like to see with atypical antipsychotic agents, they do give a sense that a drug like clozapine would be an effective maintenance treatment agent.

Risperidone

Maintenance treatment using risperidone has been less studied. Addington et al.[29] used a mirror-image study to observe hospitalization rates in patients who were treated with risperidone. The 27 patients who completed the 1-year trial averaged 106 days of hospitalization in the year before risperidone treatment and only 85 days of hospitalization during the year on risperidone treatment. In a similar design, Albright et al.[30] reported a 58% (N = 99) reduction in hospital days during the prospective year on risperidone treatment compared with the year before risperidone.

Figure 2. Time Maintaining Response to Olanzapine (Olz) vs. Placebo*



*Data from reference 31 (North American double-blind trial).
[a]Time maintaining a sufficiently reduced level of psychopathology such that hospitalization is not required. Olz-L = 2.5, 5, or 7.5 mg/day; Olz-M = 7.5, 10, or 12.5 mg/day; Olz-H = 12.5, 15, or 17.5 mg/day.

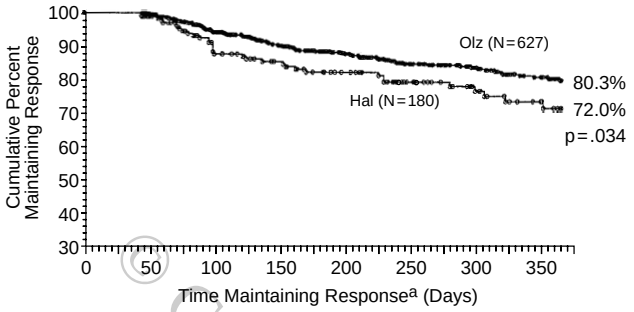
Olanzapine

Fourth-generation maintenance treatment studies with olanzapine were conducted as an extension of studies that looked at the efficacy of acute treatment of olanzapine versus placebo.[31] Patients who were responders after a 6-week acute treatment phase were allowed to continue in a double-blind fashion on their medication for up to 1 year. The 1-year average survival rate (maintaining a sufficient reduced level of psychopathology such that hospitalization was not required) of patients on 5, 10, or 15 mg daily of olanzapine was 71.4% versus 30.1% on placebo in 1 study (Figure 2). This demonstrated that olanzapine was more effective than placebo in preventing psychotic relapses that lead to hospitalization.

Olanzapine has been compared with conventional antipsychotics in preventing relapses that lead to hospitalization. In pooled data from 3 studies in which olanzapine was compared with haloperidol,[32] patients who had established a conservative 40% reduction in Brief Psychiatric Rating Scale scores after 6 weeks of treatment were followed double-blind for a year. Olanzapine demonstrated a consistent and persistent reduced risk of relapse versus haloperidol (Figure 3). Both drugs were effective in preventing relapse, but olanzapine did have a statistically significant advantage over haloperidol.

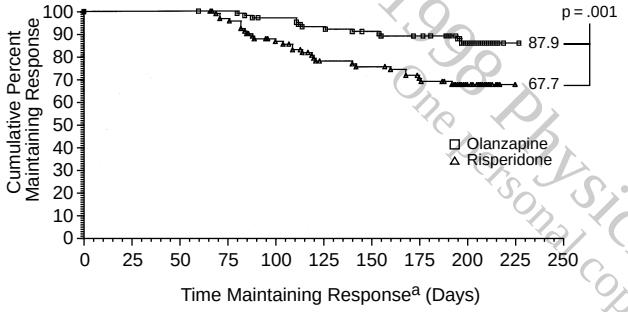
Olanzapine also has been compared with another atypical antipsychotic in preventing relapse. In a recently completed study,[33] a survival analysis was performed to estimate time maintaining response out to 28 weeks for

Figure 3. Time Maintaining Response to Olanzapine (Olz) vs. Haloperidol (Hal)*



*Data from reference 32 (pooled data from 3 studies).
[a]Time maintaining a sufficiently reduced level of psychopathology such that hospitalization is not required.

Figure 4. Time Maintaining Response to Olanzapine vs. Risperidone*

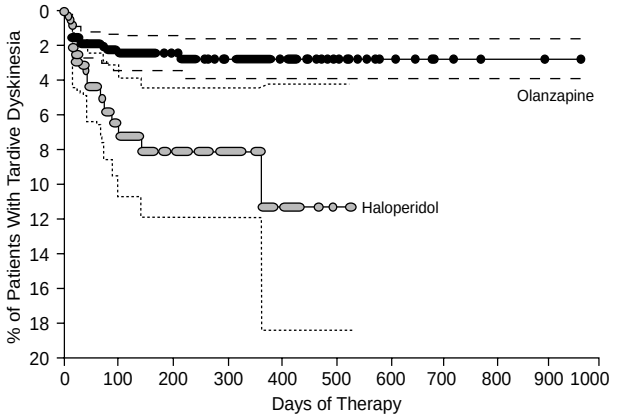


*Data from reference 33.
[a]Response defined as ≥ 20% improvement in PANSS total at week 8 (N_{olz} = 105, N_{ris} = 94). Relapse defined as ≥ 20% worsening + CGI ≥ 3 after 8 weeks.

patients on olanzapine or risperidone therapy. Only patients who showed improvement in the Positive and Negative Syndrome Scale (PANSS) total score of at least 20% from baseline at week 8 and who continued past week 8 were included in the analysis. Kaplan-Meier survival curves depicting time to a significant symptom exacerbation (≥ 20% worsening in PANSS total score and Clinical Global Impressions-Severity of Illness Scale ≥ 3) were constructed. The 2 survival curves were significantly different (p = .001) and illustrated that more patients in the olanzapine group maintained their clinical response than patients in the risperidone group (Figure 4). The estimated percentage of patients maintaining their acute response at 28 weeks was 87.9% for the olanzapine treatment group versus 67.7% for the risperidone treatment group.

In addition to demonstrating efficacy as a maintenance treatment, olanzapine has been associated with a reduced risk of developing tardive dyskinesia.[34] At 1 year, significantly fewer patients developed tardive dyskinesia, as defined by the Schooler-Kane research diagnostic criteria, when they were exposed to olanzapine treatment versus

Figure 5. Tardive Dyskinesia Survival Analysis for Double-Blind Olanzapine and Haloperidol Patients*



*Data from reference 34.

haloperidol treatment. The 1-year incidence rate was found to be approximately 0.5% with olanzapine as compared with approximately 7.5% with haloperidol. Figure 5 depicts the Kaplan-Meier survival curves of time to onset of tardive dyskinesia as a function of duration of exposure to each treatment.

CONCLUSION

In conclusion, conventional antipsychotic drugs have provided a significant therapy for the long-term management of schizophrenia. Unfortunately, in many cases this therapy also presented the patient with an untenable choice between psychotic relapse or unbearable side effects. Atypical antipsychotic drugs seem to have an equivalent, or even superior, maintenance treatment efficacy as inferred from available limited studies. Findings from olanzapine research, demonstrating an apparent reduced risk of tardive dyskinesia, offer the hope that new maintenance treatments may be better tolerated by patients as well.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril), fluphenazine (Prolixin and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

REFERENCES

1. Davis JM. Overview: maintenance therapy in psychiatry, I: schizophrenia. Am J Psychiatry 1975;132:1237–1245
2. Bartko G, Maylath E, Herczeg I. Comparative study of schizophrenic patients relapsed on and off medication. Psychiatry Res 1987;22(3):221–227
3. Hogarty GE, Ulrich RF, Mussare F, et al. Drug discontinuation among long term, successfully maintained schizophrenic outpatients. Dis Nerv Syst 1976;37(9):494–500
4. Johnson DA. The duration of maintenance therapy in chronic schizophrenia. Acta Psychiatr Scand 1976;53:298–301
5. Dencker SJ, Lepp M, Malm U. Do schizophrenics well adapted in the community need neuroleptics? a depot neuroleptic withdrawal study. Acta

Psychiatr Scand Suppl 1980;279:64–76
6. Cheung HK. Schizophrenics fully remitted on neuroleptics for 3–5 years—to stop or continue drugs? Br J Psychiatry 1981;138:490–494
7. Johnson DA. Long-term maintenance treatment in chronic schizophrenia: some observations on outcome and duration. Acta Psychiatr Belg 1981;81 (2):161–172
8. Wistedt B. A depot neuroleptic withdrawal study: a controlled study of the clinical effects of the withdrawal of depot fluphenazine decanoate and depot flupenthixol decanoate in chronic schizophrenic patients. Acta Psychiatr Scand 1981;64:65–84
9. Kane JM. Outcomes: relapse and tardive dyskinesia. In: Syllabus and Proceedings Summary of the 150th Annual Meeting of the American Psychiatric Association; May 17–22, 1997; San Diego, Calif. No. 2C:263
10. Glazer WM, Morgenstern H, Doucette JT. Predicting the long-term risk of tardive dyskinesia in outpatients maintained on neuroleptic medications. J Clin Psychiatry 1993;54:133–139
11. Kane JM, Woerner M, Sarantakos S. Depot neuroleptics: a comparative review of standard, intermediate, and low-dose regimens. J Clin Psychiatry 1986;47(5, suppl):30–33
12. Marder SR, Van Putten T, Mintz J, et al. Low- and conventional-dose maintenance therapy with fluphenazine decanoate: two-year outcome. Arch Gen Psychiatry 1987;44(6):518–521
13. Johnson DA, Ludlow JM, Street K, et al. Double-blind comparison of half-dose and standard-dose flupenthixol decanoate in the maintenance treatment of stabilised out-patients with schizophrenia. Br J Psychiatry 1987; 151:634–638
14. Hogarty GE, McEvoy JP, Munetz M, et al. Dose of fluphenazine, familial expressed emotion, and outcome in schizophrenia: results of a two-year controlled study. Arch Gen Psychiatry 1988;45:797–805
15. Kane JM, Davis JM, Schooler NR, et al. A one-year comparison of four dosages of haloperidol decanoate. Schizophr Res 1993;9:239–240
16. Schooler NR, Keith SJ, Severe JB, et al. Relapse and rehospitalization during maintenance treatment of schizophrenia: the effects of dose reduction and family treatment. Arch Gen Psychiatry 1997;54:453–463
17. Kane JM, Rifkin A, Woerner M, et al. Low-dose neuroleptic treatment of outpatient schizophrenics, I: preliminary results for relapse rates. Arch Gen Psychiatry 1983;40:893–896
18. Carpenter WT Jr, Hanlon TE, Heinrichs DW, et al. Continuous versus targeted medication in schizophrenic outpatients: outcome results. Am J Psychiatry 1990;147:1138–1148. Correction 1991;148:819
19. Herz MI, Glazer WM, Mostert MA, et al. Intermittent versus maintenance medication in schizophrenia: two-year results. Arch Gen Psychiatry 1991; 48:333–339
20. Jolley AG, Hirsch SR, Morrison E, et al. Trial of brief intermittent neuroleptic prophylaxis for selected schizophrenic outpatients: clinical and social outcome at two years. BMJ 1990;301(6756):837–842
21. Gaebel W, Frick U, Kopcke W, et al. Early neuroleptic intervention in schizophrenia: are prodromal symptoms valid predictors of relapse? Br J Psychiatry 1993;21:8–12
22. Brown GW, Birley JL, Wing JK. Influence of family life on the course of schizophrenic disorders: a replication. Br J Psychiatry 1972;121(562): 241–258
23. Vaughn C, Leff J. The measurement of expressed emotion in the families of psychiatric patients. Br J Soc Clin Psychol 1976;15(2):157–165
24. Meltzer HY, Burnett S, Bastani B, et al. Effects of six months of clozapine treatment on the quality of life of chronic schizophrenic patients. Hosp Community Psychiatry 1990;41(8):892–897
25. Miller DD, Fleming F, Holman TL, et al. Plasma clozapine concentrations as a predictor of clinical response: a follow-up study. J Clin Psychiatry 1994;55(10, suppl B):117–121
26. Kane J, Schooler N, Marder S. A six-month comparison of clozapine and haloperidol. Presented at the 35th annual meeting of the American College of Neuropsychopharmacology; December 8–13, 1996; San Juan, Puerto Rico
27. Breier A, Buchanan RW, Irish D, et al. Clozapine treatment of outpatients with schizophrenia: outcome and long-term response patterns. Hosp Community Psychiatry 1993;44(12):1145–1149
28. Essock SM, Hargreaves WA, Covell NH, et al. Clozapine's effectiveness for patients in state hospitals: results from a randomized trial. Psychopharmacol Bull 1996;32(4):683–697
29. Addington DE, Jones B, Bloom D, et al. Reduction of hospital days in chronic schizophrenic patients treated with risperidone: a retrospective study. Clin Ther 1993;15(5):917–926
30. Albright PS, Livingstone S, Keegan DL, et al. Reduction of healthcare resource utilisation and costs following the use of risperidone for patients with schizophrenia previously treated with standard antipsychotic therapy. Clin Drug Invest 1996;11(5):289–299
31. Dellva MA, Tran P, Tollefson GD, et al. Standard olanzapine versus placebo and ineffective-dose olanzapine in the maintenance treatment of schizophrenia. Psychiatr Serv 1997;48(12):1571–1577
32. Tran PV, Dellva MA, Tollefson GD, et al. Standard-dose oral olanzapine versus standard-dose oral haloperidol in the maintenance treatment of schizophrenia and related psychoses. Br J Psychiatry 1998;172:499–505
33. 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
34. Beasley C, Tollefson G, Dellva MA, et al. What is the differential risk of tardive dyskinesia with the atypical antipsychotic olanzapine? Presented at the 36th annual meeting of the American College of Neuropsychopharmacology; December 8–12, 1997; Waikoloa, Hawaii

Disclosure of Off-Label Usage

The following agents mentioned in this article are *not* indicated for maintenance treatment: clozapine, olanzapine, and risperidone.