Standard Olanzapine Versus Placebo and Ineffective-Dose Olanzapine in the Maintenance Treatment of Schizophrenia

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Objective: **Two studies compared the efficacy of standard-dose oral olanzapine (5 to 15 mg a day) with placebo and with ineffective-dose olanzapine (1 mg a day) in maintenance therapy of schizophrenia.** ***Methods:*** **The studies were 46-week double-blind extensions of multicenter studies that assessed the efficacy of olanzapine in the acute treatment of schizophrenia. Subjects were 120 adults who met *DSM-III-R* criteria for schizophrenia with an acute exacerbation and who had a minimum score of 24 on the Brief Psychiatric Rating Scale, who had responded to acute therapy (defined as at least a 40 percent reduction in the BPRS score from baseline or a score of 18 or less during up to six weeks of treatment), and who were outpatients at their last acute-phase visit. Relapse was defined as hospitalization for psychopathology. Relapse risk was analyzed using Kaplan-Meier survival analysis and life table analysis. Patients who relapsed were discontinued from the studies.** ***Results:*** **In the first study (N=58), patients in the standard-dose olanzapine group experienced a significantly lower relapse risk (p=.002) over one year than patients treated with placebo. The estimated one-year risk of relapse with olanzapine was 28.6 percent, compared with 69.9 percent with placebo. Results were similar in the second study (N=62); patients treated with standard-dose olanzapine had a significantly reduced risk of relapse (p=.018) over one year compared with patients treated with ineffective-dose olanzapine. The estimated one-year risks of relapse were 19.6 percent for standard-dose olanzapine and 45.5 percent for ineffective-dose olanzapine.** ***Conclusions:*** **Olanzapine is superior to placebo and ineffective-dose olanzapine in the maintenance therapy of schizophrenia.** (***Psychiatric Services*** **48:1571–1577, 1997)**

The importance of maintenance therapy for schizophrenia has been well documented (1,2). Antipsychotic maintenance therapy has been found to prevent relapse and rehospitalization in a substantial proportion of patients (1–6). In a recent review of 66 studies of antipsychotic withdrawal, Gilbert (2) found the reported rate of relapse to be from 0 to 100 percent (mean=46.6 percent) over periods of observation from two weeks to 24 months (mean=6.3 months). However, Davis and associates (1) have noted that all patients with schizophrenia will relapse within three years when not treated with some form of antipsychotic medication.

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Olanzapine is a thienobenzodiazepine antipsychotic. It has a broad neurotransmitter receptor affinity profile, including substantial affinity for dopamine D_4, D_2, D_1, and D_3; serotonin 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, and 5-HT_6; muscarinic cholinergic m_1-m_5; alpha$_1$-adrenergic; and histamine H_1 receptors. Olanzapine has greater potency in the antagonism of serotonergic systems than dopaminergic systems (7–10). With chronic administration, its activity is regionally selective; that is, it inhibits firing rates in the mesolimbic dopamine (A_{10}) pathway while exhibiting minimal effect on striatal dopamine (A_9) neurotransmission (10–15).

In two well-controlled blinded studies of acute treatment, olanzapine in the dose range of 5 to 20 mg a day has exhibited significantly greater efficacy than placebo in the reduction of overall psychopathology, positive psychotic symptoms, and negative symptoms (16,17). In this same dose range it has also demonstrated superior efficacy to haloperidol in reducing overall psychopathology in one acute treatment study (18) and in improving negative symptoms in two acute treatment studies (16,18). The efficacy of olanzapine in acute treatment at a dose of 1 mg a day is not significantly different from that of placebo (17).

Although the efficacy of antipsychotics in the acute treatment of schizophrenia has been demonstrated, it is also important to determine their efficacy in the prevention of re-

lapse. Three strategies have commonly been used in maintenance therapy for schizophrenia: continuing the patient on standard therapy (the dosage used for acute therapy) (19,20), continuing the patient on low-dose therapy (21–28), and using antipsychotic medication intermittently (29–32). As reviewed by Kane and Lieberman (19), nine studies comparing continuous standard-dose therapy with placebo demonstrated clear evidence of the maintenance efficacy of standard antipsychotic therapy. Another study comparing the efficacy of standard doses of five different antipsychotic agents and placebo showed that after two years in the study, 70 percent of placebo-treated patients had relapsed compared with 58 percent of patients receiving active medication (20). As further evidence, five studies that compared continuous standard-dose therapy with low-dose maintenance treatment showed that the incidence of treatment failure was higher in patients receiving continuous low-dose maintenance therapy than in those receiving continuous treatment with standard doses of antipsychotic medication (21–28). In the majority of the studies, this difference was statistically significant.

In addition, studies of intermittent therapy using fixed drug administration schedules with drug-free days (29,30) or a targeted approach with medication administered only during periods of emerging relapse or symptom exacerbation (31,32) showed that patients receiving continuous standard-dose therapy were much less likely than those receiving intermittent therapy to experience treatment failure.

This paper reports the efficacy results of the long-term double-blind extension phases of two controlled studies comparing the effectiveness of standard-dose olanzapine with placebo and a very low dose of olanzapine in the maintenance therapy of schizophrenia. These two studies also afforded an opportunity to compare the long-term efficacy of olanzapine with that of haloperidol. Results of the haloperidol comparison will be presented elsewhere. Long-term safety data will also be presented elsewhere.

Methods

North American double-blind olanzapine trial (study 1)

This study compared the efficacy of three dose ranges of olanzapine (5±2.5 mg a day, 10±2.5 mg a day, and 15±2.5 mg a day) with placebo and with one dose range of haloperidol (15±5 mg a day). Subjects were men and women between the ages of 18 and 65 who met *DSM-III-R* criteria (33) for schizophrenia with an acute exacerbation and who had a minimum total score of 24 on the Brief Psychiatric Rating Scale (BPRS) (34). The BPRS has 18 items; each item is scored from 0 to 6, with higher scores indicating greater symptom severity. Details of the acute treatment phase of this study have been described previously (16).

To be eligible for the 46-week double-blind extension and for inclusion in the analyses, patients had to have responded to acute therapy and had to be an outpatient at the last acute-phase visit. Response to acute therapy was defined as a decrease in the total BPRS score of at least 40 percent from baseline or a score of 18 or less during up to six weeks of therapy. In study 1, a total of 45 patients treated with olanzapine and 13 patients treated with placebo met eligibility criteria.

During the extension, patients were seen every two weeks. At each visit, severity of illness was evaluated using the BPRS, the Scale for the Assessment of Negative Symptoms (SANS) (35), the Clinical Global Impressions (CGI)—Severity and Improvement scale (36), and the Patient Global Impression scale (PGI) (36). They were also evaluated for extrapyramidal symptoms using the Simpson-Angus Scale (37), the Barnes Akathisia Scale (38), and the Assessment of Involuntary Movement Scale (36). In addition, laboratory analyses, including urinalysis, serum chemistry, hematology, and serum prolactin, were performed.

International double-blind olanzapine trial (study 2)

The study compared treatments identical to those in study 1 except that a very low dose of olanzapine (1 mg a day) replaced placebo. Patients enrolled in the six-week acute phase of study 2 met inclusion and exclusion criteria identical to those in study 1. In study 2, the BPRS score was extracted from the Positive and Negative Syndrome Scale (PANSS) (39). Details of the acute treatment phase of this study have been described previously (40).

Eligibility criteria for the 46-week double-blind extension and for inclusion in the analyses were the same as in study 1. Forty-eight patients treated with standard-dose olanzapine and 14 patients treated with very-low-dose olanzapine (1 mg a day) met these criteria. Assessments during the study 2 extension were similar to those in study 1.

All patients entering the double-blind extensions of study 1 and study 2 had the opportunity to complete one year of double-blind therapy. In both studies, investigators could adjust the olanzapine dose upward or downward within the assigned narrow dose range (5 mg) as clinically indicated.

Statistical methods in both studies

All analyses were done on an intent-to-treat basis; that is, all patients were included in the groups to which they were randomly assigned, even when they did not strictly adhere to the protocol. SAS procedures were used to perform all statistical analyses (41). For all analyses, main effects were tested at a two-tailed alpha level of .05. No repeated measures were used in the analyses of continuous data.

Baseline patient and illness characteristics were summarized for each treatment group. Frequencies were analyzed using Pearson's chi square test. Means were analyzed using an analysis of variance (ANOVA) with the term for treatment included in the model. Patient disposition, including reasons for discontinuation and relapse, were compared between treatment groups using Pearson's chi square test. Baseline severity of illness measured by the BPRS total score was compared between treatment groups using the ANOVA model with the terms treatment and investigator (study 1) or treatment and geographic region (study 2).

The mean modal maintenance dose

of medication was calculated as the average of the dose taken for the greatest number of days by each patient during study participation.

Kaplan-Meier survival analysis was used to estimate the risk of relapse during one year of long-term maintenance therapy. Relapse was defined as hospitalization for psychopathology. Data from study 1 were used for comparison of the pooled olanzapine treatment groups (5±2.5 mg a day, 10±2.5 mg a day, and 15±2.5 mg a day) with the placebo treatment group. Data from study 2 were used for comparison of the comparable pooled olanzapine treatment groups (5±2.5 mg a day, 10±2.5 mg a day, and 15±2.5 mg a day) with the very-low-dose olanzapine treatment group (1 mg a day).

Kaplan-Meier survival curves for time to relapse were compared between treatment groups. In computing the survival curves, patients who were discontinued from the study for a reason other than hospitalization due to psychopathology were included in the analyses as right-censored observations. The risk of relapsing by 365 days (one year of double-blind therapy) was estimated from the Kaplan-Meier curves. Comparisons of the survival curves were performed using the log-rank test.

Life table analyses evaluated the percentage of patients who relapsed during each two-week interval during the double-blind extension through one year of treatment. The numbers and percentages of patients hospitalized at each week of observation from among those remaining in the study at that week were computed. A Mantel-Haenszel chi square test was used to compare the survival patterns of olanzapine with placebo and with very-low-dose olanzapine.

Results

North American double-blind olanzapine trial (study 1)

Patient and illness characteristics. As shown in Table 1, no significant differences were observed between patients enrolled in the olanzapine and placebo treatment groups in terms of gender, ethnic background, age, or illness characteristics.

Kaplan-Meier survival analysis.

Table 1

Characteristics of patients in the double-blind extension phase of the North American double-blind olanzapine trial (study 1)

Characteristic	Olanzapine (N=45) N	Olanzapine (N=45) %	Placebo (N=13) N	Placebo (N=13) %	Test statistic	df	p
Sex					χ^2=.14	1	.708
Male	36	80	11	85			
Female	9	20	2	15			
Race					χ^2=1.04	4	.904
Caucasian	34	76	10	77			
African	5	11	2	15			
East or Southeast Asian	1	2	0	—			
Hispanic	3	7	1	7			
Other	2	4	0	—			
Age (mean±SD)	34.8±10.1		36.4±7.7		F=.31	1,56	.581
Schizophrenia subtype					χ^2=2.94	2	.230
Disorganized	4	9	0	—			
Paranoid	27	60	6	46			
Undifferentiated	14	31	7	54			
Course of schizophrenia							
Subchronic with acute exacerbation	9	20	2	15	χ^2=.14	1	.708
Chronic with acute exacerbation	36	80	11	85			
Age of onset of psychosis (mean±SD years)	23.9±7.0		23.2±5.8		F=.12	1,56	.731
Length of current episode (mean±SD days)	69.2±88.4		74.8±117.4		F=.04	1,56	.852
Duration of illness (mean± SD years)	10.9±7.7		13.3±7.7		F=1.00	1,56	.321
N previous episodes					χ^2=2.71	4	.607
Less than ten	27	60	10	77			
Ten to 19	8	18	1	8			
20 to 29	5	11	2	15			
40 to 49	1	2	0	—			
50 or more	4	9	0	—			
Total score on the Brief Psychiatric Rating Scale at baseline (mean±SD)	14.2±6.7		13.7±8.4		F=.07	1,42	.789

Figure 1

Kaplan-Meier survival plot of time to relapse for patients taking olanzapine and placebo in study 1

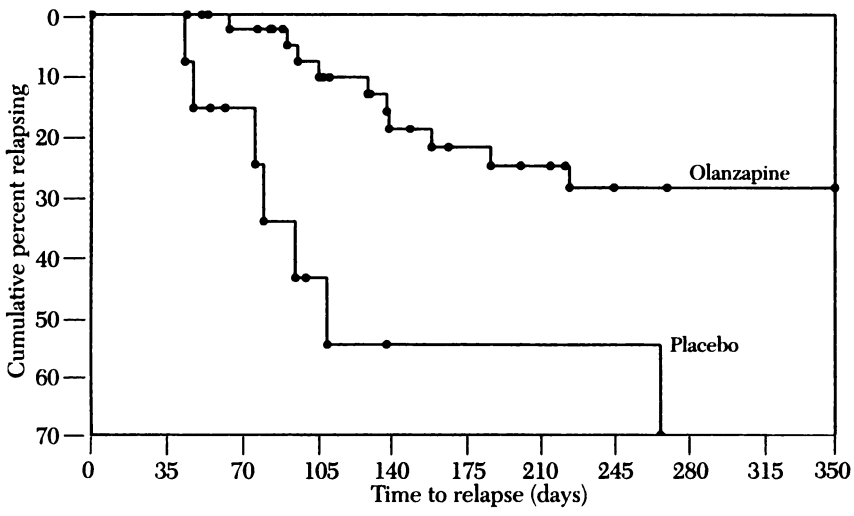

Table 2

Characteristics of patients in the double-blind extension phase of the international double-blind olanzapine trial (study 2)

Characteristic	Olanzapine (N=48) N	%	Very-low-dose olanzapine (N=14) N	%	Test statistic	df	p
Sex					χ^2=.56	1	.453
Male	29	60	10	71			
Female	19	40	4	29			
Race					χ^2=1.30	3	.729
Caucasian	40	83	13	93			
African	4	8	1	7			
Western Asian	2	4	0	—			
Other	2	4	0	—			
Age (mean±SD years)	37.5±12.6		35.5±11.6		F=.27	1,60	.604
Schizophrenia subtype					χ^2=8.04	2	.018
Disorganized	5	10	6	43			
Paranoid	31	65	5	36			
Undifferentiated	12	25	3	21			
Course of schizophrenia					χ^2=2.35	2	.309
Unspecified	1	2	0	—			
Subchronic with acute exacerbation	11	23	6	43			
Chronic with acute exacerbation	36	75	8	57			
Age of onset of psychosis (mean±years)	24.8±8.3		27.4±10.2		F=1.00	1,60	.322
Length of current episode (mean±SD days)	92.8±253.3		106.1±109.4		F=.04	1,60	.850
Duration of illness (mean±SD years)	12.7±10.8		8.1±9.2		F=2.10	1,60	.153
N previous episodes					χ^2=.92	4	.921
Less than ten	42	88	13	93			
Ten to 19	1	2	0	—			
20 to 29	3	6	1	7			
30 to 39	1	2	0	—			
More than 50	1	2	0	—			
Total score on the Brief Psychiatric Rating Scale at baseline (mean±SD)	15±7.2		11.6±6.8		F=2.86	1,49	.097

Figure 2

Kaplan-Meier survival plot of time to relapse for patients taking olanzapine and an ineffective dose of olanzapine in study 2

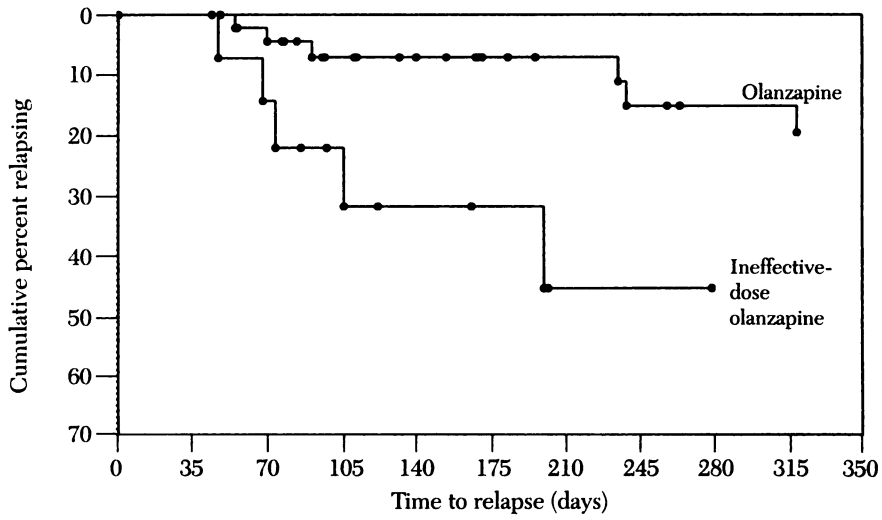

Figure 1 illustrates the Kaplan-Meier survival curves depicting time to relapse for the olanzapine treatment group and the placebo treatment group. The mean modal maintenance dose for olanzapine-treated patients was 12.1±4.9 mg a day. When the two curves were compared over their entirety, a statistically significant difference was observed (log-rank χ^2=9.80, df=1, p=.002). The estimated risk of relapse for the two groups by one year, calculated from these survival curves, was 28.6 percent for olanzapine-treated patients and 69.9 percent for placebo-treated patients.

Life table analysis. Fewer relapses were observed among patients treated with olanzapine than among patients treated with placebo. There was a statistically significant difference between the survival patterns favoring olanzapine-treated patients (Mantel-Haenszel χ^2=9.37, df=1, p=.002).

Patient disposition. Of the olanzapine-treated patients, 17 (38 percent) completed the full one-year extension period without relapse, and ten (22 percent) relapsed. Five patients (11 percent) were discontinued for modification of treatment, two (4 percent) because of an adverse event, five (11 percent) for not meeting criteria or noncompliance, and four (9 percent) as the result of a personal decision; two patients (4 percent) were lost to follow-up.

Two of the placebo-treated patients (15 percent) completed the extension phase without relapse, and seven (54 percent) relapsed. Two (15 percent) were discontinued for modification of treatment and two (15 percent) as the result of a personal decision.

Patients in the olanzapine treatment group experienced a significantly lower rate of relapse (22 percent) than patients treated with placebo (54 percent) (Pearson's χ^2=4.87, df=1, p=.027).

International double-blind olanzapine trial (study 2)

Patient and illness characteristics. As Table 2 shows, no significant differences were observed between patients enrolled in the standard-dose and very-low-dose olanzapine treatment groups in gender, ethnic back-

ground, or age. The overall difference in schizophrenia subtype between the two groups was statistically significant. The percentage of patients diagnosed as having disorganized schizophrenia was higher in the very-low-dose olanzapine group than in the standard-dose olanzapine group (43 percent versus 10 percent), and the percentage of patients diagnosed as having paranoid schizophrenia was higher in the standard-dose group than in the very-low-dose group (65 percent versus 36 percent). All other illness characteristics were similar for the two groups.

Kaplan-Meier survival analysis. Figure 2 illustrates the Kaplan-Meier survival curves depicting time to relapse for the standard-dose olanzapine group and the very-low-dose olanzapine group. The mean modal maintenance dose for patients treated with the standard dose was 11.5±4.4 mg a day. When the two curves were compared over their entirety, a statistically significant difference was observed (log-rank $\chi^2=5.59$, df=1, p=.018). The estimated risk of relapse for the two groups by one year, calculated from these survival curves, was 19.6 percent for standard-dose olanzapine-treated patients and 45.5 percent for very-low-dose olanzapine-treated patients.

Life table analysis. Fewer relapses were observed among patients treated with the standard dose than patients treated with 1 mg of olanzapine a day. A statistically significant difference was found between the survival patterns favoring standard-dose olanzapine-treated patients (Mantel-Haenszel $\chi^2=5.59$, df=1, p=.018.)

Patient disposition. Of the patients treated with standard-dose olanzapine, 16 (33 percent) completed the full one-year extension period without relapse, and six (13 percent) relapsed. Five patients (10 percent) were discontinued for modification of treatment, ten (21 percent) because of an adverse event, five (10 percent) for not meeting criteria or noncompliance, and four (8 percent) as the result of a personal decision; one patient (2 percent) was lost to follow-up, and one (2 percent) had a satisfactory response and was judged not to need antipsychotic medication.

Of the patients treated with 1 mg of olanzapine a day, two (14 percent) completed the extension phase without relapse, and five (36 percent) relapsed. One patient (7 percent) was discontinued for modification of treatment, two (14 percent) because of an adverse event, two (14 percent) for not meeting criteria or noncompliance, and two (14 percent) as the result of a personal decision.

Patients in the standard-dose olanzapine-treated group experienced a significantly lower rate of relapse (13 percent) than patients treated with very-low-dose olanzapine (36 percent) (Pearson's $\chi^2=4$, df=1, p=.045).

Discussion and conclusions

The results of these two olanzapine studies are consistent with regard to the estimated one-year risk of relapse shown in the Kaplan-Meier survival curves. In study 1 an estimated one-year risk of 28.6 percent was found for patients treated with standard doses of olanzapine, compared with a risk of 69.9 percent for placebo-treated patients (log-rank $\chi^2=9.8$, df=1, p=.002). In study 2, patients treated with standard-dose olanzapine had an estimated one-year risk of 19.6 percent, compared with 45.5 percent for patients treated with very-low-dose olanzapine (1 mg a day) (log-rank $\chi^2=5.59$, df=1, p=.018).

Comparison of the results of studies of maintenance therapy for schizophrenia is difficult, even when the studies use the same antipsychotic agent and route of administration. Notable differences in study methods that make comparisons difficult include the potential for adjustment of treatment in the study; the allowance of concomitant medications; the method of selecting patients, especially the length of time patients have been stable on standard medication before study entry; and the definition of relapse. The definition of relapse is of particular concern because some studies have permitted dose increases to treat worsening of symptoms without categorizing a patient as having relapsed, while other studies have not.

With the exception of one study by Goldstein and colleagues (21), previous maintenance studies (19,20,22–30) have been classic two-phase rerandomization studies in which all patients were first determined to be stable on standard-dose therapy and were then randomly assigned to receive lower-dose therapy or to continue standard therapy. Greenhouse and associates (42,43) have noted that such a study design is biased in favor of patients not switched to the alternative therapy. Patients treated during the experimental phase with the treatment to which they had responded and on which they had demonstrated stability without relapse would be expected to show fewer relapses than those who had switched.

In the study by Goldstein and colleagues (21) and in the olanzapine studies, assignment of patients to treatment groups was fixed at the outset of acute treatment. The design is comparable to that advocated by Greenhouse and associates (42,43), who have suggested that a maintenance study design that does not rerandomize treatment after acute response avoids the bias inherent in rerandomization designs. The design is consistent with clinical practice in which patients are continued on therapy as long as response is maintained. In a study with such a design, less relapse would be expected among patients on placebo or ineffective-dose olanzapine compared with patients switched to placebo or ineffective-dose olanzapine in a rerandomization design study. For this reason, any design bias in the olanzapine trials would be expected to reduce rather than increase treatment differences.

Another difference between the olanzapine studies and all of the previous studies (19–29) except one (21) is that in the olanzapine studies, patients entered the maintenance phase with minimal stabilization. Because of the shorter duration of stability among study patients, higher relapse rates would be expected for all treatment groups. Goldstein and colleagues (21), who evaluated patients during the first six weeks after discharge, noted that a previous study showed that 45 percent of patients were readmitted during the first six months after discharge, and that 31 percent of those readmissions oc-

curred within the first three to four weeks after discharge. Among patients who had not been stabilized for a substantial length of time, a higher discontinuation rate would be expected than among stable patients who demonstrated compliance with therapy before selection for study participation.

As in other studies, patients in the olanzapine studies were required to show substantial clinical response during the six weeks of acute treatment in order to be included in the maintenance phases. Although the requirement was comparable to that in other maintenance studies, it may differ from the clinical situation in which improvement, but only partial response, results in a patient's being maintained on a given agent. Results presented here, therefore, may not be generalizable to that clinical situation.

In comparing these results with those of previous investigations, consideration must also be given to the dosage adjustments permitted. Some study designs permitted dosages to be increased by as much as twofold to treat worsening symptoms without requiring patients to be classified as having relapsed. In the olanzapine studies, investigators could adjust dosages of individual patients upward, but only within the narrowly prescribed dose range (50 percent for the 5±2.5 mg a day group, 25 percent for the 10±2.5 mg a day group, and 17 percent for the 15±2.5 mg a day group). Patients had to be discontinued from the olanzapine studies to receive a dosage that exceeded their assigned range. Both the actual relapse rate and the rate of discontinuation for modification of treatment, especially the latter, might have been reduced among the standard-dose olanzapine treatment groups had a dosage increase of 100 percent been allowed as in the studies by Kane and colleagues (25), Marder and associates (22,23), and Hogarty and colleagues (24).

In the majority of recent studies of maintenance therapy for schizophrenia, depot formulations of antipsychotic medication were used to eliminate noncompliance as a possible reason for treatment failure. The olanzapine studies used oral medication. Because compliance cannot be ensured with oral therapy, risk of relapse may have been increased for standard-dose olanzapine-treated patients in these olanzapine studies.

In the olanzapine studies, all patients were seen more frequently (every two weeks) than in the majority of the other studies discussed here. More frequent observation provided investigators with a greater opportunity to observe patients' symptoms and detect clinical changes that might not otherwise have come to their attention. The increased frequency of observation had the potential to increase observed relapse rates because of increased sensitivity to clinical deterioration. Alternatively, the increased frequency of clinical contact may have delivered an element of support that served to reduce the risk of relapse.

Results of the two olanzapine studies are consistent in the estimated one-year risk of relapse.

The apparently high rates of discontinuation for reasons other than relapse or of completion without relapse may also limit the generalizability of study results. Factors likely to have contributed are the minimal stabilization time before entry into the maintenance phase and the minimal dosage adjustment allowed. Despite these contributory factors, the discontinuation rates for the olanzapine studies are not substantially dissimilar from those of other studies. In studies of standard-dose treatments, Kane and coworkers (25) reported a 47 percent discontinuation rate at one year, Marder and associates (22,23) reported 19 percent at one year, and Hogarty and colleagues (24) reported 24 percent at two years for the standard-dose treatment arms. The rates in the olanzapine studies were 40 percent in study 1 and 54 percent in study 2. It must be recalled that these rates included patients who were discontinued (11 percent and 10 percent, respectively) because they could not receive additional medication within the study.

The operational definition of treatment failure has varied substantially across previous studies, and multiple definitions of failure have been used. Among low-dose studies, hospitalization was used by Goldstein and associates (21) as an explicit criterion for treatment failure and was analyzed as a secondary variable in the studies by Marder and coworkers (23) and Hogarty and associates (24). Hospitalization was an explicit criterion for treatment failure in all of the intermittent-dose studies (29–32). The studies reported here also used this criterion: relapse was defined as hospitalization for psychopathology. Change in symptom severity may be complementary to definitive categorical outcomes such as hospitalization. However, abrupt decompensation leading to hospitalization (presumably associated with increases in scores on symptom severity scales) may elude the formal rating process. Hospitalization is a robust and easily identifiable indicator of clinical status and meaningful outcome variables.

The results of these analyses of long-term maintenance therapy with standard doses of olanzapine among patients with schizophrenia show that olanzapine is superior to placebo and ineffective-dose olanzapine in preventing relapse. Despite differences in study methods, such as in selection of patients and definition of relapse, relapse rates in the olanzapine studies are consistent with and compare favorably with those in other studies that used standard-dose therapy. When differences in study methods are taken into consideration, discontinuation rates in the olanzapine studies also compare favorably with those in other studies using standard-dose therapy. ♦

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References

1. Davis JM, Kane JM, Marder SR, et al: Dose response of prophylactic antipsychotics. Journal of Clinical Psychiatry 54(suppl 3):24–30, 1993
2. Gilbert PL, Harris MJ, McAdams LA, et al: Neuroleptic withdrawal in schizophrenic patients. Archives of General Psychiatry 52:173–188, 1995
3. Schooler NR: Maintenance medication for schizophrenia: strategies for dose reduction. Schizophrenia Bulletin 17:311–324, 1991
4. Schooler NR: Reducing dosage in maintenance treatment of schizophrenia. British Journal of Psychiatry 163(suppl 22):58–65, 1993
5. Kane JM, Marder SR: Psychopharmacologic treatment of schizophrenia. Schizophrenia Bulletin 19:287–302, 1993
6. Johnstone EC, Geddes J: How high is the relapse rate in schizophrenia? Acta Psychiatrica Scandinavica 89(suppl 382):6–10, 1994
7. Bymaster FP, Calligaro DO, Falcone JF, et al: Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology 14:87–96, 1996
8. Bymaster FP, Hemrick-Luecke SK, Perry KW, et al: Neurochemical evidence for antagonism by olanzapine of dopamine, serotonin, α_1-adrenergic, and muscarinic receptors in vivo in rats. Psychopharmacology 124:87–94, 1996
9. Fuller RW, Snoddy HD: Neuroendocrine evidence for antagonism of serotonin and dopamine receptor by olanzapine (LY 170053), an antipsychotic drug candidate. Research Communications in Chemical Pathology and Pharmacology 77:87–93, 1992
10. Moore NA, Tye NC, Axton MS, et al: The behavioral pharmacology of olanzapine, a novel "atypical" antipsychotic agent. Journal of Pharmacology and Experimental Therapeutics 262:545–551, 1992
11. Arnt J: Differential effects of classical and newer antipsychotics on the hypermotility induced by two dose levels of D-amphetamine. European Journal of Pharmacology 283:55–62, 1995
12. Cools AR, Prinssen EPM, Ellenbroek BA: The olfactory tubercle as a site of action of neuroleptics with an atypical profile in the paw test: effect of risperidone, prothipendyl, ORG 5222, sertindole, and olanzapine. Psychopharmacology 119:428–439, 1995
13. Robertson GS, Fibiger HC: Effects of olanzapine on regional C-Fos expression in rat forebrain. Neuropsychopharmacology 14: 105–110, 1996
14. Stockton ME, Rasmussen K: Electrophysiological effects of olanzapine, a novel atypical antipsychotic on A_9 and A_{10} dopamine neurons. Neuropsychopharmacology 14: 97–104, 1996
15. Stockton ME, Rasmussen K: Olanzapine, a novel atypical antipsychotic, reverses d-amphetamine-induced inhibition of midbrain dopamine cells. Psychopharmacology 124:50–56, 1996
16. Beasley C, Tollefson G, Tran P, et al: Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 14:111–123, 1996
17. Beasley C, Sanger T, Satterlee W, et al: Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacology 124:159–167, 1996
18. Tollefson G, Beasley C, Tran P, et al: Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. American Journal of Psychiatry 154:457–465, 1997
19. Kane JM, Lieberman JA: Maintenance pharmacotherapy in schizophrenia, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven Press, 1987
20. Crow TJ, MacMillan JF, Johnson AL, et al: A randomised controlled trial of prophylactic neuroleptic treatment. British Journal of Psychiatry 148:120–127 1986
21. Goldstein MJ, Rodnick EH, Evans JR, et al: Drug and family therapy in the aftercare of acute schizophrenics. Archives of General Psychiatry 35:1169–1177, 1978
22. Marder SR, Van Putten T, Mintz J, et al: Costs and benefits of two doses of fluphenazine. Archives of General Psychiatry 41:1025–1029, 1984
23. Marder SR, Van Putten T, Mintz J, et al: Low- and conventional-dose maintenance therapy with fluphenazine decanoate: two-year outcome. Archives of General Psychiatry 44:518–521, 1987
24. Hogarty GE, McEvoy JP, Munitz M, et al: Dose of fluphenazine, familial expressed emotion, and outcome in schizophrenia. Archives of General Psychiatry 45:797–805, 1988
25. Kane JM, Rifkin A, Woerner M, et al: Low-dose neuroleptic treatment of outpatient schizophrenics. Archives of General Psychiatry 40:893–896, 1983
26. Kane JM, Rifkin A, Woerner M, et al: High-dose versus low-dose strategies in the treatment of schizophrenia. Psychopharmacology Bulletin 21:533–537, 1985
27. Kane JM, Woerner M, Sarantakos S: Depot neuroleptics: a comparative review of standard, intermediate, and low-dose regimens. Journal of Clinical Psychiatry 47(suppl 5):30–33, 1986
28. Johnson DAW, 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. British Journal of Psychiatry 151:634–638, 1987
29. Carpenter WT, Hanlon TE, Heinrichs DW, et al: Continuous versus targeted medication in schizophrenic outpatients: outcome results. American Journal of Psychiatry 147:1138–1148, 1990
30. Herz MI, Glazer WM, Mostert MA, et al: Intermittent vs maintenance medication in schizophrenia. Archives of General Psychiatry 48:333–339, 1991
31. Jolley AG, Hirsch SR, McRink A, et al: Trial of brief intermittent neuroleptic prophylaxis for selected schizophrenic outpatients: clinical outcome at one year. British Medical Journal 298:985–990, 1989
32. Pietzcker A, Gaebel W, Köpcke W, et al: Intermittent versus maintenance neuroleptic long-term treatment in schizophrenia: 2-year results of a German multicenter study. Journal of Psychiatric Research 27:321–339, 1993
33. Diagnostic and Statistical Manual of Mental Disorders, 3rd ed, rev. Washington, DC, American Psychiatric Association, 1987
34. Woerner MG, Mannuzza S, Kane JM: Anchoring the BPRS: an aid to improved reliability. Psychopharmacology Bulletin 24: 112–117, 1988
35. Andreasen NC: Negative symptoms in schizophrenia. Archives of General Psychiatry 39:784–788, 1982
36. Guy W (ed): ECDEU Assessment Manual for Psychopharmacology, revised ed. DHEW pub (ADM)76-338. Rockville, Md, National Institute of Mental Health, 1976
37. Simpson GM, Angus JW: A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavica 212(suppl):11–19, 1970
38. Barnes TR: A rating scale for drug-induced akathisia. British Journal of Psychiatry 154:672–676, 1989
39. Kay SR, Opler LA, Fiszbein A: Positive and Negative Syndrome Scale (PANSS) Manual. North Tonawanda, NY, Multi-Health Systems, 1992
40. Beasley CM, Hamilton SH, Crawford AM, et al: Olanzapine versus haloperidol: acute-phase results of the international double-blind olanzapine trial. European Neuropsychopharmacology 7:125–137, 1997
41. SAS/STAT User's Guide, Version 6, 4th ed, vol 1 and 2. Cary, NC, SAS Institute, 1989
42. Greenhouse JB, Meyer MM: A note on randomization and selection bias in maintenance therapy clinical trials. Psychopharmacology Bulletin 27(3):225–229, 1991
43. Greenhouse JB, Stangl D, Kupfer DJ, et al: Methodologic issues in maintenance therapy clinical trials. Archives of General Psychiatry 48:313–318, 1991