Annals of Clinical Psychiatry, Vol. 15, No. 1, March 2003 (© 2003)

Rehospitalization Risk With Second-Generation and Depot Antipsychotics[1]

Robert R. Conley, MD,[2,4] Deanna L. Kelly, PharmD, BCPP,[2] Raymond C. Love, PharmD, BCPP,[3] and Robert P. McMahon, PhD[2]

Decreasing hospital admissions is important for improving outcomes for people with schizophrenia. Second-generation antipsychotics (SGAs) are better tolerated for long-term therapy than traditional medications and may contribute to a lower rehospitalization risk, but have not been compared to depot forms with regard to long-term outcomes. This study evaluates the risk of readmission in patients discharged from six State of Maryland inpatient mental health facilities between Jan. 1, 1997 and Dec. 31, 1997 on clozapine ($N = 41$), risperidone ($N = 149$), and olanzapine ($N = 103$). These patients were compared with those discharged from the two largest state facilities during the same time period on fluphenazine decanoate ($N = 59$) or haloperidol decanoate ($N = 59$). One-year readmission risk (measured by Kaplan–Meier survival analysis with Holm's adjustment for multiple comparison on Log Rank tests) were 10% for clozapine, 12% for risperidone, and 13% for olanzapine. These risks were not significantly lower than the readmission risk for fluphenazine decanoate (21%) but were significantly lower than haloperidol decanoate (35%) for all three SGAs. Demographic and clinical variables did not predict readmission for any of the medications. In patients with similar demographic and clinical characteristics, 1-year risk of readmission for patients treated with SGAs were at least comparable to the 1-year risk for patients receiving fluphenazine decanoate and lower than the risk for patients treated with haloperidol decanoate. SGAs may provide better long-term prognoses and outcomes for patients with schizophrenia.

KEY WORDS: schizophrenia; depot antipsychotics; atypical antipsychotics; rehospitalization.

INTRODUCTION

Decreasing hospital admissions is important for improving outcomes for people with schizophrenia. The decision to readmit patients usually indicates symptomatology or behavior that can no longer be safely managed in the community or is intolerable outside of an institutional setting. Predicting which patients with schizophrenia will be rehospitalized by clinical estimates or models, often performs no better than chance (1, 2). Clinical presentation during an inpatient stay is the usual criterion used to predict readmission. In reality, inpatient symptomatology may have less to do with rehospitalization risk than patterns of behavior and social circumstances influencing recovery (2). Nonetheless, the best predictors of readmission are history of previous psychiatric hospital admission (3, 4), comorbid substance abuse (5, 6), low family support and therapeutic alliances (7, 8), and nonadherence with medications (6, 9).

Depot preparations of traditional antipsychotic medications were developed to aid with adherence to long-term drug therapy. The reported benefits

[1]Preliminary results of this paper were presented at the International Congress on Schizophrenia Research, Santa Fe, NM, April 17–21, 1999, and the American College of Neuropsychopharmacology held in Las Croabas, Puerto Rico, December 14–18, 1998.

[2]Maryland Psychiatric Research Center, University of Maryland, Baltimore, Maryland.

[3]Baltimore School of Pharmacy, University of Maryland, Baltimore, Maryland.

[4]To whom correspondence should be addressed at Maryland Psychiatric Research Center, Box 21247, Baltimore, Maryland 21228; e-mail: rconley@mprc.umaryland.edu.

1040-1237/03/0300-0023/1

of depot preparations include the elimination of bioavailability problems, assurance of drug delivery, and a better strategy for low-dose therapy. Disadvantages include the potential for irreversible and unpleasant side effects, the time required to reach optimal dosing, the inability to immediately withdraw the drug if side effects develop, and patients' feelings of being controlled (10, 11). Although clinicians widely believe that depot preparations increase patient adherence, there has been debate as to the extent to which long-acting injectable antipsychotics decrease relapse and rehospitalization rates when compared with oral agents. Schooler *et al.* (12) reported that in 290 patients randomly assigned to fluphenazine decanoate or oral fluphenazine, the risk of rehospitalization between the groups at 1 year following discharge was not significantly different (28%). Two recent meta analyses (Cochrane Database Reviews, 2000; CD000307, CD001361) concluded that the current literature is not sufficient to discern differences in relapse or rehospitalization rates between depot and oral agents (without therapy) in the first year following discharge. Furthermore, little convincing evidence exists to suggest large improvements in adherence rates with long-term therapy employing depot formulations.

Despite the paucity of data from well-designed studies demonstrating superior outcomes for depot antipsychotics versus oral therapy the Patient Outcomes Research Team (PORT), the Texas Medication Algorithm Project (TMAP), and consensus treatment guidelines recommend that clinicians strongly consider depot medications for patients who are nonadherent to oral medications (13–15). Evidence-based guidelines for the use of depot antipsychotics are important as the use of depot preparations is widespread. Within state mental health facilities, 12–39% of all patients receive traditional antipsychotics in depot formulations (16). However, the overall use of depot medications in outpatient settings in the United States is low, representing only about 2% of all antipsychotic prescriptions (IMS health, Retail and Provider Perspective, December 2000). The best predictor for a depot prescription rather than an oral antipsychotic is a previous prescription for a depot. Younger patients, African Americans, and Hispanics are more likely than Caucasians and older patients to receive depot antipsychotics (16, 17). Tavcar *et al.* (18) recently published a naturalistic report regarding antipsychotic selection. Those who appeared to have a more chronic illness, i.e., longer lengths of hospitalizations, were more likely to receive Second generation antipsychotics (SGAs) versus either depot or traditional oral antipsychotics. Thus, the variables affecting the selection of depot agents versus SGAs have not been well studied for outcome differences. Furthermore, the determinants governing prescriber selection between the agents have not been well characterized. However, this data suggests that more chronically hospitalized patients may be treated with SGAs as opposed to depot agents.

SGAs were developed to provide more effective and tolerable treatments for those who suffer from schizophrenia. In fact, these agents may improve cognitive performance and secondary negative symptoms, offer some enhanced efficacy in treatment-resistant schizophrenia, and possess a lower risk for extrapyramidal side effects and tardive dyskinesia (19). Although it has not been systematically studied, SGAs theoretically should increase adherence due to their better risk to benefit profile than traditional antipsychotics. Because nonadherence is as high as 50% with traditional medications (20), these agents may reduce relapse and rehospitalization rates.

The estimated annual risk of rehospitalization with the use of SGAs in the United States has ranged from 13–20%. A 20% relapse rate was reported for olanzapine as compared to 28% for haloperidol at 1 year (21). Previously reported data from our group during risperidone's first year of release found a 17% rehospitalization risk at 1 year following discharge (22). Conley *et al.* (22) and Essock *et al.* (23) reported risks of rehospitalization with clozapine of 13% and 18%, respectively. These are all lower than the previously published risks of 28–50% with traditional oral agents (21, 23, 24). A recent report from Israel examining rehospitalization for 2 years following discharge found the rehospitalization risk with SGAs to be significantly lower than those with conventional antipsychotics (31–33% vs. 48%). This separation was evident even in a chronically ill population of patients that had failed at least two previous antipsychotic trials (25). Hogarty and Ulrich (26) and Schooler *et al.* (27) have reported that rates of readmission appear to be lower with depot agents (19–28%) than oral agents but only when used in conjunction with personal, social, or family therapy. In fact, rates may be reduced by as much as 50% compared with medication and standard care when psychosocial treatment is included (26). Previously, we analyzed rehospitalization risk for those taking depot in a small cohort from 1994 to 1995 and reported rehospitalization risk between 21 and 36% for the first year following discharge (28).

There have been no direct comparisons between SGAs and depot agents with regards to risk of rehospitalization. This report compares rehospitalization in patients discharged on an SGA (clozapine, risperidone, olanzapine) with those discharged on fluphenazine or haloperidol decanoate between January 1, 1997 and December 31, 1997.

METHODS

To evaluate the effect of newly introduced SGAs on rehospitalization, inpatient records from six major public psychiatric hospitals in the State of Maryland (accounting for over 90% of publicly funded beds in the State) were collected prospectively in the State of Maryland Outcomes Monitoring Program. These facilities treat a diverse group of ethnically and geographically different patients. All patients who were successfully discharged on either SGAs (clozapine, risperidone, olanzapine) or depot antipsychotics (fluphenazine or haloperidol decanoate) between January 1, 1997 and December 31, 1997 were included in the study. Data from decanoate prescriptions were included only for two of the largest facilities in the State that account for more than 50% of the beds. Pharmacy records at these facilities were identified for patients prescribed a depot during the study period, as patients taking depots are not currently included in the antipsychotic database. All groups included in the study were treated within the same mental health system, however, depot and SGA were independent samples. Patients treated with depot agents and included in this study did not differ in baseline chronicity measures, represented the majority of depots prescribed in State psychiatric inpatient facilities, and were believed to be representative of the entire population prescribed depots.

A successful discharge was defined as a patient who was begun on medication and discharged on that same drug within one admission. After discharge, all patients were followed by their routine-care providers, mostly in community mental health centers around the State of Maryland. Readmission was defined as rehospitalization in any public hospital for a psychiatric condition. All patients were followed for possible readmission until August 1998. Those who were rehospitalized in a private facility were not captured as a readmission in this study. However, readmission to a nonpublic facility within this time interval is thought to be rare. Private readmissions were less than 2% of all readmissions from this group in prior analyses. Furthermore, all psychiatric readmissions needed for patients discharged within 60 days from a State mental health facility in Maryland are required to be readmitted to the hospital of last admission.

This protocol was approved by the University of Maryland and State of Maryland Institutional Review Boards. A waiver was granted for informed consent due to the low-risk nature of the study.

Only patients with a DSM-IV diagnosis of schizophrenia were included in this report. In order to verify diagnoses, two members of the investigative team performed chart reviews to compare the most recent diagnoses from monthly individual treatment plans with computerized records. Only those patients with ages greater than 12 years were included. Eleven patients with extremely long lengths of stay (z scores greater than 3.29, 7–15 years) were excluded from this analysis.

The distribution of time to rehospitalization for each treatment was estimated using the Kaplan–Meier (29) method of survival analysis, with follow-up censoring at August 1998. Unadjusted comparisons of time to discharge among treatments were performed using the log-rank test (30). The Cox proportional hazards regression model (31) was used to perform comparisons among treatments after adjusting for covariates thought to affect time to readmission (age, race, sex, dose, length of stay prior to medication start, and length of time on drug prior to discharge). Treatments were compared on demographic variables using chi-square tests or analysis of variance (ANOVA), using simulation-based adjustment for multiple pairwise comparisons for the ANOVAs. Holm's modification of the Bonferroni procedure (32) was used to adjust p-values for multiple two-sided comparisons and to maintain an overall Type I error rate of $\alpha = 0.05$. With this procedure, the 10 p-values from the pairwise comparisons were sorted in order from the smallest to largest. The null hypothesis corresponding to the smallest p-value would be rejected if that p-value was $<0.05/10$. We would continue until the kth smallest p-value was $>0.05/k$, at which point no further pairwise differences would be considered significant. For the k smallest p-value, the adjusted p-value was calculated as the minimum of 1.0 or k multiplied by that p-value.

RESULTS

During 1997, 293 schizophrenic patients meeting the criteria listed above were discharged from the

six State of Maryland psychiatric inpatient facilities on SGAs (clozapine, $N = 41$; risperidone, $N = 149$; olanzapine, $N = 103$). During that same period, 59 patients each receiving haloperidol and fluphenazine decanoate were discharged. Demographic and clinical variables for these groups can be found in Table 1. No statistically significant differences between the medication groups were demonstrated in regards to age, sex distribution, previous number of prior admissions, and the length of time in the hospital prior to receiving the current medication. Significantly more African Americans than Caucasians received depots as compared to the SGAs. The groups differed in the length of time on the medication prior to being discharged. Patients receiving clozapine and fluphenazine decanoate had significantly longer times of inpatient treatment prior to discharge as compared to the other drug groups. Although clozapine treated patients appeared to have had a somewhat more chronic hospitalization course prior to treatment with clozapine, these variables did not reach significance.

Annual risk of rehospitalization were 10% for those in the clozapine group, 12% for the risperidone group, 13% for the olanzapine group, 21% for the fluphenazine decanoate group, and 35% for those receiving haloperidol decanoate. This data is presented in Fig. 1. There were no significant differences among the SGAs with regards to risk for rehospitalization. Using the log-rank test with Holm's procedure to adjust for multiple comparisons, statistically significant differences in rehospitalization risk were present between those groups receiving haloperidol decanoate versus risperidone ($\chi^2 = 14.8$, $p = 0.0001$, adjusted $p = 0.001$), olanzapine ($\chi^2 = 11.1$, $p = 0.0009$, adjusted $p = 0.008$) and clozapine ($\chi^2 = 7.5$, $p = 0.006$, adjusted $p = 0.049$). Observed risk for rehospitalization for the SGAs were smaller than for the fluphenazine decanoate group, but none of these differences were statistically significant, even without adjusting for multiple comparisons. Differences in time to rehospitalization between the two decanoate groups also were not statistically significant ($\chi^2 = 2.7$, $p = 0.099$, adjusted $p = 0.70$). Corresponding to these differences in time to rehospitalization, mean time in the community for patients who were rehospitalized was 195 days with clozapine, 163 days with risperidone, and 170 days with olanzapine. Time in the community was lower but not significantly so with depot treatment (149 and 140 days for fluphenazine or haloperidol decanoate, respectively) (See Table 2).

Age, sex, race, dose, length of stay prior to medication start, and length of time on drug prior to discharge were not found to be risk factors for readmission by the Cox proportional hazards regression model. Additionally, we reran sex and race as main effect tests to further delineate any baseline variables in relation to rehospitalization risk and also found no significant results.

DISCUSSION

The literature is sparse with regards to risk of relapse and rehospitalization of patients receiving SGAs. This study is 1 of the first to directly compare 1-year rehospitalization frequency among SGAs compared to depot agents. Clozapine, risperidone, and olanzapine were all associated with similar annual risks of rehospitalization, 10, 12, and 13%, respectively. The depot preparations were associated with rehospitalization rates of 21–35%. The rates with fluphenazine were not significantly different than those with the SGAs, while haloperidol decanoate was associated with a substantially higher rate than that of the newer agents. The rates of rehospitalization in the SGA groups in this study are consistent with the 13–20% reported elsewhere (21–23), while the rates with depot antipsychotics without psychosocial treatment are known to be greater than 20% annually (26–28). Therefore, depot use as a control group in this study, validated previous data that SGAs appear to be associated with lower rates of rehospitalization even in patients who are severely ill and receiving clozapine (20).

Our current findings are important, because one would expect that the depot agents would lead to more favorable outcomes or at least perform equally to SGAs by reducing the impact of nonadherence on relapse and rehospitalization. Intrinsic differences between the SGAs and traditional antipsychotics (depot and oral) may account for the favorable outcomes obtained with SGAs. Clozapine, specifically, is known to offer superior efficacy as compared to traditional medications in the treatment-resistant population (33, 34). Risperidone and olanzapine have been found to be superior to haloperidol for some symptom domains in treatment-responsive individuals with schizophrenia (35, 36). Superior response on negative and depressive symptoms may lead to greater interaction with family, therapists, and others and have a beneficial effect on one's ability to remain in the community (8). One recent study, however, found

Table 1. Demographic and Clinical Variables

	Clozapine ($N = 41$)	Risperidone ($N = 149$)	Olanzapine ($N = 103$)	Fluphenazine decanoate ($N = 59$)	Haloperidol decanoate ($N = 59$)
Age (years ± SD)	36.9 ± 9.4	38.0 ± 14.5	39.7 ± 13.7	39.9 ± 9.4	35.1 ± 8.9
Race	64% White, 28% Black	67% White, 30% Black	74% White, 25% Black	44% White, 56% Black[a]	36% White, 64% Black[b]
Sex	61% Male	63% Male	58% Male	72% Male	68% Male
Previous number of admissions in past 5 years (number ± SD)	1.7 ± 1.5	1.1 ± 1.5	1.3 ± 1.7	0.9 ± 1.2	1.1 ± 1.2
Length of time in hospital prior to starting medication (days ± SD)	309 ± 472	119 ± 287	88 ± 225	87 ± 149	111 ± 214
Length of time on drug prior to discharge (days ± SD)	299 ± 339[b]	78 ± 134	61 ± 62	220 ± 334[c]	113 ± 121
Maximum stabilized dose (mg/day ± SD)	403.8 ± 193.1	4.8 ± 2.4	16.2 ± 6.0	50.7 ± 29.3[d]	150.8 ± 108.4[d]

[a] $p < 0.01$ vs. clozapine, olanzapine, risperidone.
[b] $p < 0.05$ vs. olanzapine and risperidone, $p = 0.0644$ vs. clozapine, multitest adjusting for multiple comparisons.
[c] $p < 0.0001$ vs. risperidone, olanzapine, and haloperidol decanoate, ANOVA with adjustment for multiple comparisons.
[d] Mean milligram dose per month.

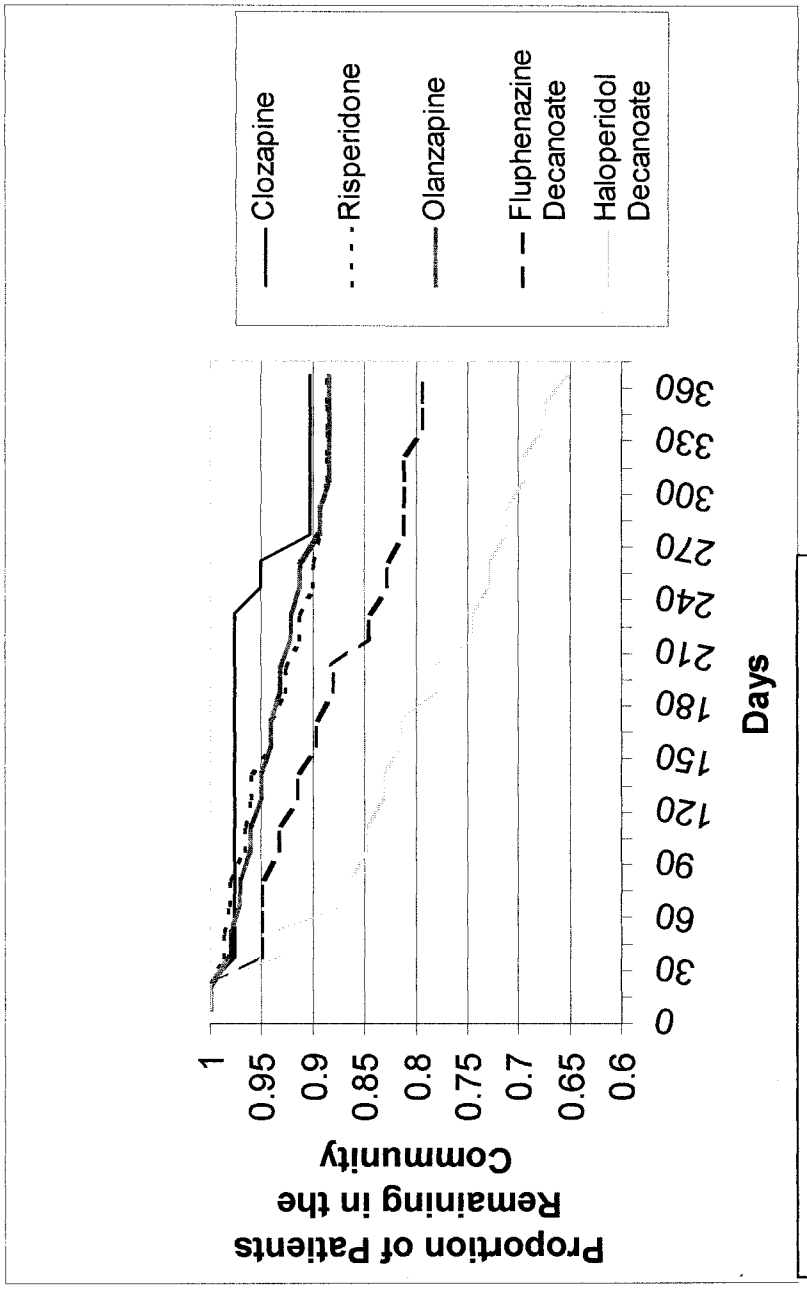

Fig. 1. Proportion of patients remaining discharged by antipsychotic.

Table 2. Time to Rehospitalization in Patients Discharged on Antipsychotic Medications

	Clozapine ($N = 41$)	Risperidone ($N = 149$)	Olanzapine ($N = 103$)	Fluphenazine decanoate ($N = 59$)	Haloperidol decanoate ($N = 59$)
Annual risk of readmission (95% CI)	10% (1–19)	12% (7–18)	13% (6–20)	21% (10–31)	35% (22–47)[a]
Mean time in the community for those rehospitalized days (days ± SD)	195.3 ± 112.7	162.6 ± 90.9	169.7 ± 105.7	148.5 ± 98.7	140.4 ± 112.6
Median time in the community for those rehospitalized days (range)	246.0 (27–262)	157.5 (7–359)	175.0 (19–345)	161.5 (0–322)	140.5 (1–358)

[a] $p < 0.05$ (Holm's adjusted p-value) vs. clozapine, risperidone, and olanzapine.

rates of rehospitalization to be higher with SGAs as compared to traditional oral agents. This study included patients from only one facility and those treated with the SGAs had longer lengths of stays and may have represented a more severe population (37).

If the depot formulation contributes little to decreasing the risk of rehospitalization for conventional antipsychotics, then SGAs may be a reasonable selection even in patients who are only partially compliant. Mahmoud *et al.* (38) reported that patients who took their prescribed risperidone only part of the time still had superior outcomes compared to conventional antipsychotics. Additionally, risperidone use following depot treatment in a multicenter observational study was favored by patients by a margin of 83–23%. This study also found significant improvements in PANSS and GAF scores as well as improvements in Parkinson and dyskinesia symptoms. Sixty-five percent of patients with schizophrenia considered risperidone a better choice than traditional depot agents (39).

While differences in the rehospitalization risks between the decanoates were not statistically significant ($p = 0.09$), we did observe a lower frequency of rehospitalization among patients treated with fluphenazine decanoate compared to haloperidol. When compared to SGAs, the haloperidol decanoate group had a higher risk of rehospitalization than the fluphenazine decanoate group. Others have reported similar results and this finding may be due to higher haloperidol dosing being used or the higher rates of side effects that have been reported (40, 41). Higher rates of side effects could contribute to nonadherence. We were unable to determine a relationship between dosage and rehospitalization, even after sorting subjects into low, moderate, and high dosing groups and analyzing outcomes.

In our study, a significantly greater proportion of African Americans versus Caucasians received decanoate injections (60%) as compared to SGAs (28%). While it is true that there are genetic polymorphisms that may lead to pharmacokinetic differences between African Americans and Caucasians, (42, 43) there is little supporting evidence that these differences in the metabolism of haloperidol and fluphenazine leads to differences in response. Furthermore, Tunnicliffe *et al.* (44) found that ethnicity was not a factor that affected medication adherence with depot injections. Rather, the majority of data on ethnicity indicates usage differences are due to clinician bias. Citrome *et al.* (16) reported that African Americans and Hispanics were significantly more likely to be prescribed depot as compared to other antipsychotics than were Caucasians. Additionally, Segal *et al.* (45) reported that in an emergency setting, less time for evaluations and more oral and injectable psychiatric medications were given to African Americans than to Caucasians. Additionally, higher doses of antipsychotics are often given to African Americans, which may contribute to their higher risk for tardive dyskinesia (46). Nonetheless, neither race nor different prescribing practices in the racial groups has been shown to affect the risk of readmission.

Although this study lacks some of the benefits of a prospective double-blind clinical trial, the naturalistic design has its own advantages. The results of the study represent the "real-world" use of these medications. Controlled trials limit the generalizability of findings and often will include much more patient contact than exists in the outpatient setting. Practitioners prescribed these antipsychotics and discharged patients based on their own clinical judgement. One limitation of this study is the lack

of an oral conventional antipsychotic control group. However, because the risk for rehospitalization associated with both the SGAs and the depot agents are similar to other published reports, we have no reason to suspect that readmission rates in Maryland State facilities for patients receiving conventional antipsychotics would be any different from published rates of 28–50%. The Maryland system does not currently collect antipsychotic utilization data for oral conventional antipsychotics. Other limitations include the inability to measure some variables such as substance abuse status and level of family support. These variables, however, were not believed to be largely different between groups as a high percentage of people with schizophrenia abuse substances and family support in this setting is relatively low, overall. While the rationale for use of particular antipsychotics remains unknown, SGA are recommended over conventional agents in patients with comorbid substance abuse for numerous reasons and we believe these treatment recommendations would have been applicable to a majority of patients (47).

As new antipsychotics enter the marketplace, it is important to critically evaluate the benefits of these agents compared to conventional antipsychotics. This study demonstrates that the risk of rehospitalization for the SGAs, clozapine, risperidone, and olanzapine are at least comparable to depot fluphenazine and superior to haloperidol decanoate for the prevention of rehospitalization. Implications of this finding may include better long-term prognosis and quality of life for these patients as well as potential reductions in overall treatment costs for patients receiving SGAs. As new depot formulations of SGAs enter the marketplace in the next few years, it will become necessary to examine the impact of these agents on relapse and the cost of care.

ACKNOWLEDGMENT

Support and funding for this work was in part by the Theodore and Vada Stanley Foundation and Intervention Research Center Grant MH-40279.

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